Development of reusable, biologically compatible olefin metathesis initiators

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Development of Reusable, Biologically Compatible Olefin Metathesis Initiators

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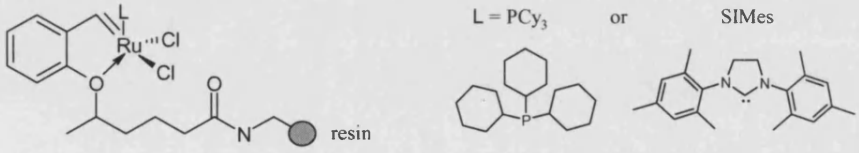
Abstract

Olefin metathesis is a carbon redistribution in which unsaturated carbon-carbon double bonds rearrange in the presence of metal-carbene complexes. One of our overall aims was to use olefin metathesis under biological conditions to rapidly generate molecules in the presence of biological targets, such as proteins, in order to identify potential inhibitors.

With this in mind, we designed a polymer-supported catalyst by extending the ligand whilst retaining its stability and introducing recyclability. Initial synthesis of the vinyl ligand proved to be problematic, thus commercially available 2-(prop-1-enyl)phenol was used but the corresponding initiator showed poor recyclability in olefin metathesis. A new route was developed towards the vinyl ligand confirming the superiority of the vinyl-supported initiator. Further study showed that the recapture of the ruthenium methylidene active species is faster with vinyl ligand than with the propenyl one, explaining the difference in the reactivity and decomposition of the two initiators.



To improve the efficiency of our pre-catalyst, a variety of ligand modifications were performed to increase the performance. A hydrophilic resin used as the solid support allowed reactions in polar solvents.

A new ligand was synthesised to be attached to Grubbs' catalyst in order to improve its efficiency in polar solvents. A functional group modification of 4,5-dihydroimidazol-2-ylidene (SIMes) ligand allowed modulation of the solubility of the catalyst. When protected, it increases the solubility in the organic phase, while deprotection increases the water-solubility of the compound.

To test the utility of these initiators, the final aim of the project was to develop synthetic methods towards fructose analogues using cross-metathesis to produce possible fructose transport inhibitors. Investigation of the reaction suggested that the alkene oxime group of the various synthetic sugars forms a complex with ruthenium catalysts, leading only to isomerisation of the substrate and inhibition of olefin metathesis.

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I would like to thank the technicians in the department for their technical support, Dr. Steven Black for recording the NMR spectra and Mr. Chris Cryer for Mass Spectrometry.

Finally, "MERCI à mes parents" for their encouragement and their continuous support from France.

Abbreviations

Ac	acetate
aq	aqueous
Ar*H*	aromatic proton (NMR)
b	broad (NMR)
Bn	benzyl
BSA	*bis*-trimethylsilylacetamide
Cbz	benzyloxycarbonyl
CM	cross-metathesis
cm	centimetre
Cy	cyclohexyl
°C	degree Celsius
d	doublet (NMR)
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMA	dimethylacetamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
δ_C	chemical shift: carbon NMR (NMR)
δ_H	chemical shift: proton NMR (NMR)
EI	electron impact (mass spectrometry)
eq	equivalent
Et	ethyl
FAB	fast atom bombardment (mass spectrometry)
h	hour(s)
Hz	hertz (NMR)
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant in Hz (NMR)
m	multiplet (NMR)

m/z	mass to charge ratio (mass spectrometry)
M	moles per litre
Me	methyl
Mes	mesityl: 2,4,6-trimethylphenyl
MHz	megahertz (NMR)
min	minutes
mp	melting point
MS	mass spectrometry
M^+/M^-	molecular ion (mass spectrometry)
$NaHCO_3$	Sodium hydrogen carbonate
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOBA	3-nitrobenzyl alcohol
pH	-log $[H^+]$
Ph	phenyl
ppm	parts per million (NMR)
q	quadruplet/quartet (NMR)
qn	quintet
RCM	ring-closing metathesis
R_f	retention factor
ROMP	ring-opening metathesis polymerization
r.t.	room temperature
s	singlet (NMR)
SIMes	saturated 1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2ylidene
t	triplet (NMR)
THF	tetrahydrofuran
TLC	thin layer chromatography
vs.	versus
ν	frequency of a signal in cm^{-1} (IR)

Contents

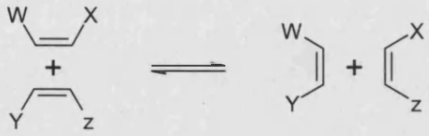
Index of Figures, Schemes, Tables and Graphs.

1.0 Introduction

1.1 Olefin metathesis

1.1.1 History

Olefin metathesis was first observed in the 1950s by researchers working for several major U.S. petrochemical companies. The workers discovered that when propylene was passed over a molybdenum-on-aluminium catalyst, a propylene-ethylene co-polymer was formed. Analysis showed that the composition of the gas formed was a mixture of propylene, ethylene and 1-butene. Calderon *et al.* at Goodyear Tyre & Rubber determined that the unexpected products were due to cleavage and reformation of the double bonds, and named the reaction "olefin metathesis"[1] (Scheme 1-1).



Scheme 1-1: Simple representation of olefin metathesis.

A number of attempts were made to determine the intermediate involved in olefin metathesis. Grubbs suggested two possibilities, a rearrangement *via* a metallacyclopentane intermediate[2] or a cyclobutane complexed to a metal carbene[3] (Figure 1-1). Pettit proposed a tetramethylene complex[4] (Figure 1-1), in which four methylene units are bonded to a central metal atom.

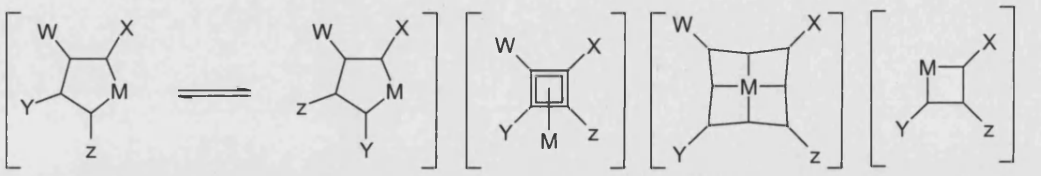


Figure 1-1: Different types of intermediates considered.

Chauvin and Hérisson suggested that olefin metathesis was initiated by a metal carbene reacting with an olefin to form a metallacyclobutane intermediate (Figure 1-1). This intermediate then breaks down to form a new metal carbene, which propagates the reaction.[5] This work was the first to explain correctly the role of metal carbenes in olefin metathesis and the rearrangement of groups around carbon-carbon double bonds.

However, it was several years before the mechanism was experimentally supported by the work of Casey and Burkhardt.[6]

In 1976, Katz reported the first use of an isolable metal-carbene complex, (diphenylcarbene)-pentacarbonyltungsten, to initiate the formation of unsymmerically substituted ethylene by olefin metathesis.[7] It was also found that this complex, together with (methoxyphenylcarbene)-pentacarbonyltungsten, initiated polymerization of various cyclic olefins such as cyclobutene and norbornene.[8,9] Subsequently, Schrock prepared carbyne tungsten complexes and studied their reactivity with various acetylenes[10] and proceeded to make high oxidation-state tungsten carbenes that led him to develop the highly active and now-renowed molybdenum carbene catalyst **1** (Figure 1-2). This work was further developed by Grubbs who introduced the highly efficient ruthenium carbene complexes **2** and **3** (Figure 1-2). Due to the increase in the number of specific catalysts, olefin metathesis became a very attractive reaction because of its tolerance towards a variety of functional groups, its reversibility and its applicability in a number of areas of chemistry.

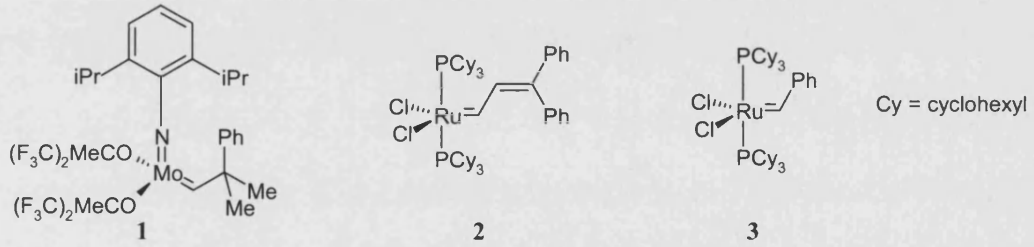


Figure 1-2: Examples of catalysts used in olefin metathesis reactions.

1.1.2 Different types and uses

Olefin metathesis is a carbon redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal-carbene complexes. With the use of efficient catalysts, this reaction is a powerful tool for the formation of carbon-carbon double bonds in chemistry as it is a quick and potentially reversible organo-metallic reaction. Three types of olefin metathesis reactions have been described: [11]

Ring-opening metathesis polymerisation reaction (ROMP) (Scheme 1-2) is a convenient route to polymers because it maintains unsaturation and allows the direct incorporation of functionality from the monomer. The functional group tolerance of

ruthenium catalysts has extended ROMP to a more diverse set of monomers.[12,13] Others have applied ROMP to attach highly functionalized hydrophilic substrates such as norbornene derivatives to sugars, amino acids, and other biological molecules.[14]

Scheme 1-2: Ring-opening metathesis polymerisation reaction **(ROMP)**.

For example, Kiessling investigated the functional properties of a new class of polyvalent carbohydrate ligands, substances prepared by ring-opening metathesis polymerization.[15] Such saccharide-substituted polymers proved to act as polyvalent ligands for the mannose/glucose-binding protein concanavalin A. Polyvalent *C*- and *O*-glycoside derivatives of the glucose or mannose configuration were generated *via* an aqueous ROMP. Kiessling also synthesised end-labelled multivalent ligands to explore cell-surface-receptor-ligand interactions (Figure 1-3).[16]

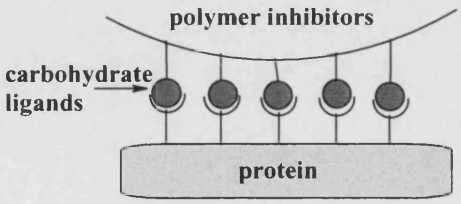
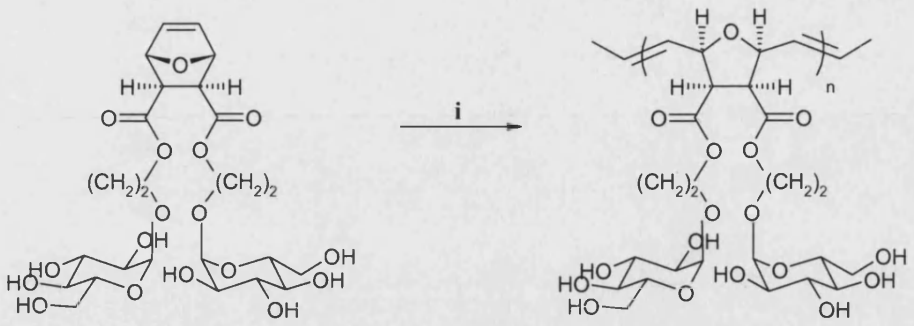


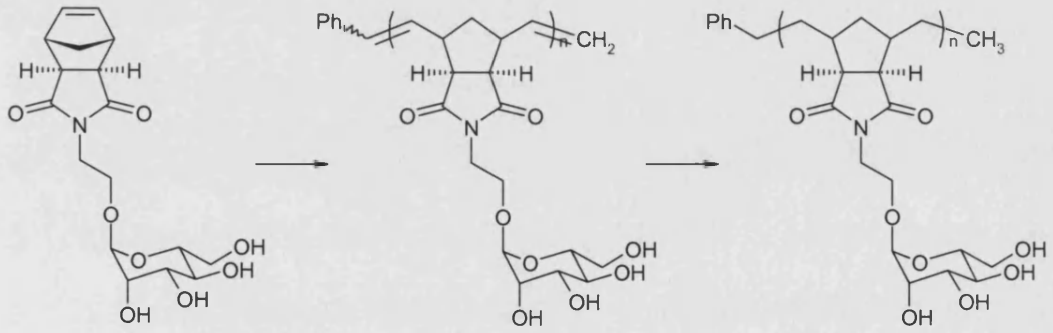
Figure 1-3: Interaction between the polymer-supported ligand and the target protein.

The corresponding bicyclic oxanorbornene derivatives were polymerized to afford glucose- and mannose-substituted *C*-glycoside neoglycopolymers. To decrease the amount of residual metal in the resulting carbohydrate-substituted materials, the polymerization was effected using a catalyst solution derived from mixing the oxanorbonene substrate and $RuCl_3$ in water. Application of the general strategy afforded the α-*O*-glycoside and α-*O*-mannoside polymers (Scheme 1-3). For each polymer, the backbone was produced as a 1:1 ratio of *cis* and *trans* alkene isomers. The activities of the polymers were assessed by comparing their ability to inhibit erythrocyte agglutination by concanavalin A. The polyvalent ligands display significant increases in functional affinity.



Scheme 1-3: Synthesis of saccharide substituted polymer inhibitors of cancanavalin A: **i**- $RuCl_3$, H_2O, 55 °C.

Kiessling used the ring-opening polymerization to generate a variety of multivalent saccharide displays in which numbers of repeat units within a set are systematically varied (Scheme 1-4). Carbohydrate polymers have emerged as important materials for the exploration of protein-saccharide interactions, which are significant components in diverse biological process.[17]



Scheme 1-4: Synthesis of multivalent saccharide displays.

More recently, two other types of reaction have become increasingly attractive due to the development of metathesis catalysts which are tolerant to many functional groups and are reactive to a large range of substrates.

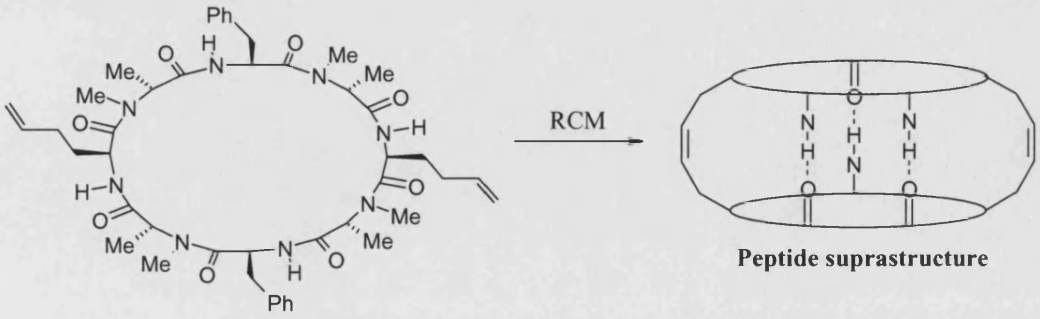
Ring-closing metathesis (RCM) (Scheme 1-5) is extremely useful for the synthesis of medium (5-8) or large (8 or more) sized rings from acyclic diene precursors. The driving force of the transformation is the release of highly volatile ethylene.

Scheme 1-5: Ring-closing metathesis **(RCM)**.

Although Schrock's molybdenum complex is suitable for RCM of basic amines, it causes problems for the conversion of certain amides or when used with α,β- or β,γ-unsaturated compounds, as the catalysts may become inhibited by intramolecular interactions with the carbonyl group. On another hand, Grubbs ruthenium catalyst **3**, which is tolerant towards a wide range of substituents, was not affected by intramolecular secondary reactions.[18]

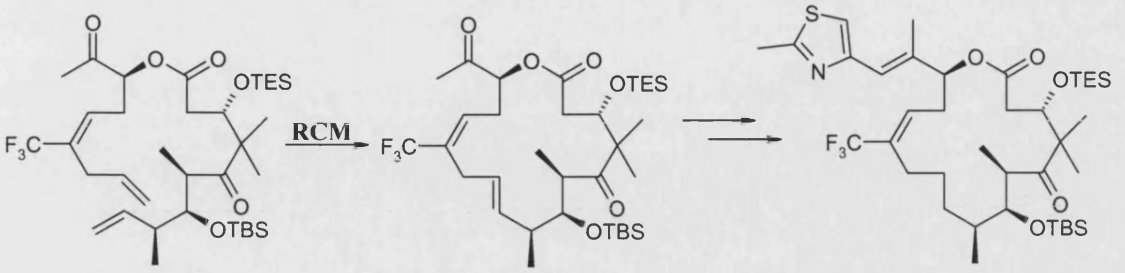
Four-membered rings cannot be obtained using such reactions because of the ring strain, although larger rings (5-8) show efficient cyclization. The synthesis of eight-membered rings is particularly challenging as the required olefins are often suitable monomers for completing ROMP. The balance between RCM and ROMP is certainly affected by ring strain but cyclizations proceed if a high degree of dilution is maintained.

Generally, larger ring systems are more readily accessible as the ring size allows the formation of *cis* and/or *trans* double bonds, due to low ring strain. The yields are not only dependent on the ring size, but also on the position of the resulting double bond. RCM using Grubbs ruthenium complex **3** has been used successfully in the synthesis of various substance classes often with a large variability in the reaction time. The formation of 13-membered rings can require a reaction time of up to five days, while the ring closure of 14-membered rings proved to be complete after a few hours. This difference in reactivity may be caused by a variation in the proximity of the two reacting alkenes. RCM was also used successfully in supramolecular chemistry for the synthesis of a 38-membered ring peptide suprastructure, which is one of the largest cyclic compounds constructed by olefin metathesis (Scheme 1-6).[19]



Scheme 1-6: Type of suprastructures synthesised *via* ring-closing metathesis.

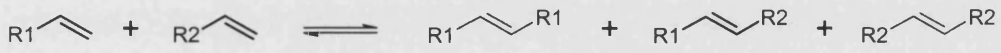
Ring-closing metathesis was also used in the early stage of the synthesis of (*E*)-9,10-dehydroepothilones (anti-cancer drug candidates) in order to close the 16-membered ring intermediate.[20]



(*E*)-9,10-dehydroepothilone

Scheme 1-7: Use of ring-closing metathesis in the synthesis of anti-cancer drug candidate.

Acyclic cross metathesis (CM) between two different olefins can afford three new types of alkenes as seen in Scheme 1-8. Terminal olefins afford gaseous ethylene, which provides the driving force of the reaction. Silylated compounds such as vinyl siloxane derivatives have found wide applications in organic synthesis when used in palladium-(0)-catalyzed C-C-coupling reactions with aryl iodides.[21] Fischer and co-workers have shown that vinylsilanes couple with alkyl vinyl ethers ($ROCH{=}CH_2$) to give CM products of general type $ROCH{=}CHSiR_3$ in high yields.[22]



Scheme 1-8: Acyclic cross metathesis **(CM)**.

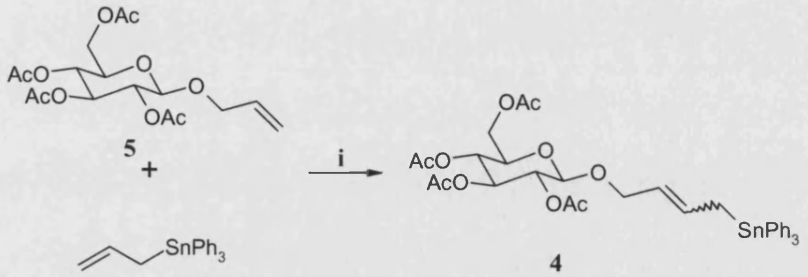
An example of CM involving well-defined ruthenium complexes and allenes has been reported[23] by Barrett and co-workers. A variety of mono-substituted allenes were treated with Grubbs catalyst **3** at 20 °C creating self-metathesised 1,3-disubstitued allene products along with polymeric material (Scheme 1-9).

Scheme 1-9: Acyclic cross metathesis of allene compounds.

CM has evolved into a flexible and powerful methodology and is used in the synthesis of biologically active compounds such as natural products[24] and carbohydrates.[25]

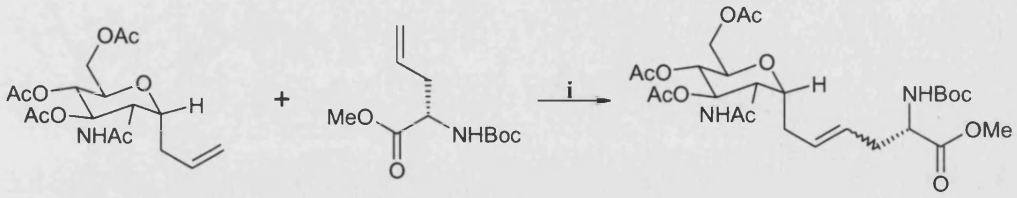
Recently, there has been a great deal of research interest in CM with a number of chemists using the technique to achieve smooth high-yielding transformations as key components of multistep selective synthesis.

For example, Blechert used olefin-cross metathesis to generate radical precursors such as compound **4** from protected propenyloxy sugar **5** and allyltriphenyl stannane. This product was used for nucleophilic additions to electrophilic carbon centres and for radical reactions (Scheme 1-10).[26]



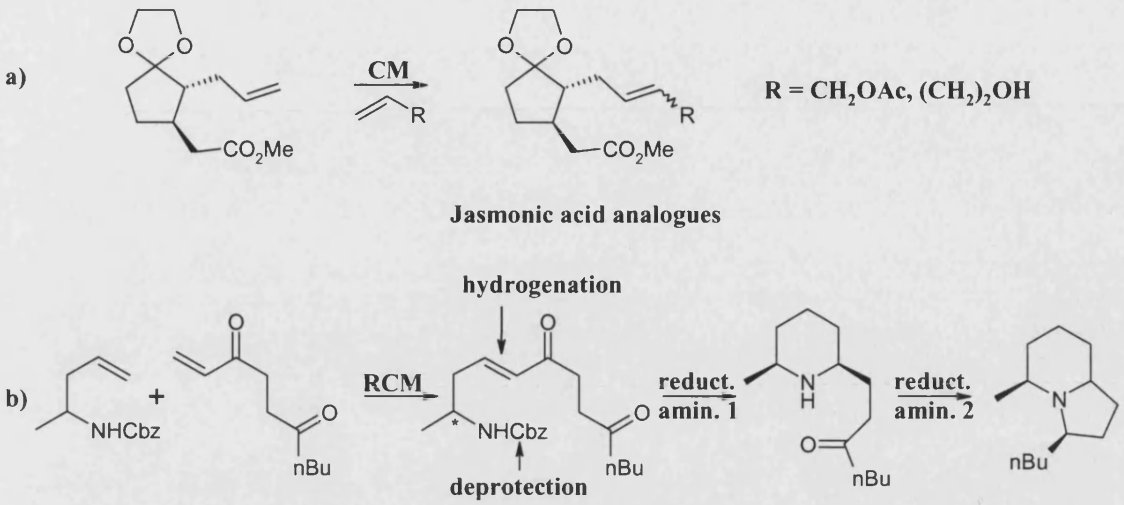
Scheme 1-10: Synthesis of radical precursors *via* cross-metathesis: **i**- Dichloromethane, **1**, 12 h, 40 °C, 67 %.

Glycoconjugates, components of cell surfaces such as glycoproteins, show correlations with a variety of disease states including a role in infection. Thus, McGarvey synthesised a library of glycoproteins *via* cross-metathesis which allows the isolation of unique glycoforms of these amino acids (Scheme 1-11).[27]



Scheme 1-11: Olefin cross-metathesis to *C*-glycoamino acids: **i**- Grubbs catalyst **3**, dichloromethane, 16 h.

As previously mentioned, cross metathesis was used in the synthesis of natural products such as analogues of jasmonic acid, a highly powerful plant hormone (Scheme 1-12, a)).[24] This reaction can also be associated to other reactions including reductive cyclization to synthesise compounds, such as indolizidine alkaloids (Scheme 1-12, b)).[28]



Scheme 1-12: **a)** Synthesis of derivatives of natural product jasmonic acid, **b)** Synthesis of indolizidine alkaloid (+)- monomorine I.

1.1.3 Mechanism

In order to develop catalysts with superior activity, stability and selectivity, the mechanism of olefin metathesis has been intensively studied by Grubbs and other groups using ruthenium complexes.[29-33] Complexes of the general formula $L(PR_3)(X)_2Ru{=}CHR'$, where L can be a phosphine or an *N*-heterocyclic carbene ligand (Figure 1-9), X is a halogen and R′ is an alkylidene moiety (Scheme 1-13). The effect of variation of ligand position has been studied.

The mechanism of the reaction proceeds in three steps: initiation, propagation and termination. Initial investigations focused on the ligand exchange of phosphine with the olefinic substrate. The substitution can occur following an associative pathway, which leads to an 18 electron olefin complex, or a dissociative pathway that leads to a 14 electron olefin complex (Figure 1-13).

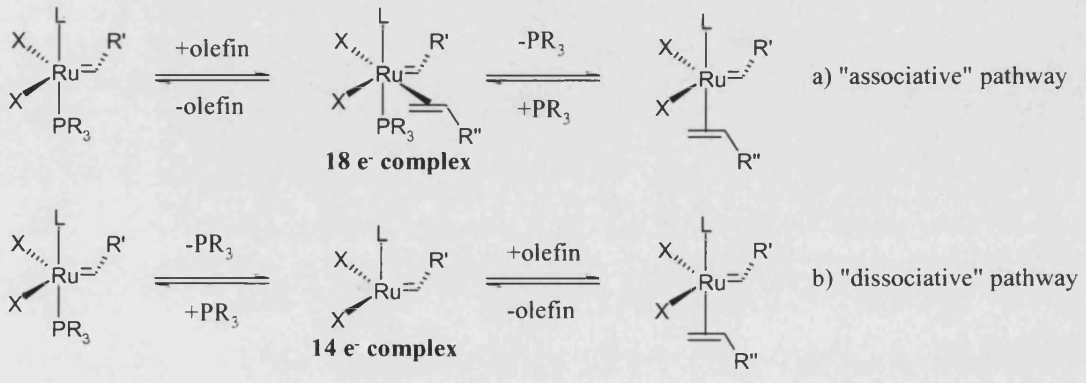
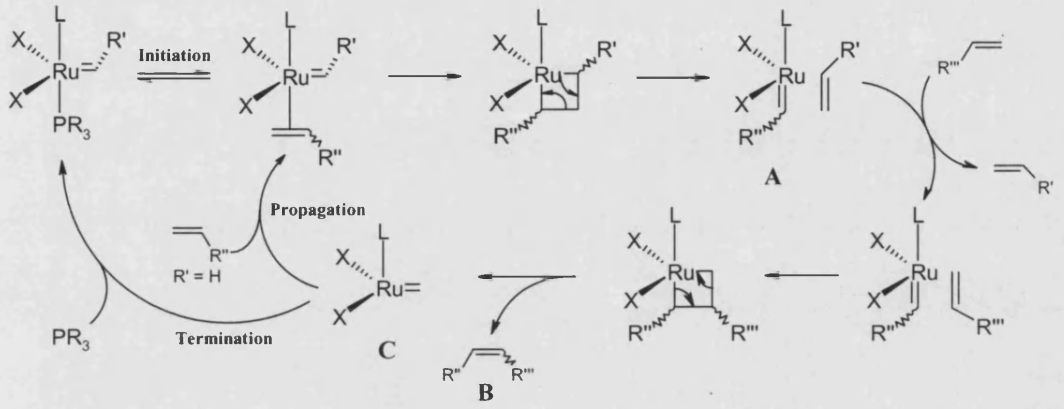


Figure 1-13: Two different pathways towards the olefin metathesis reaction.

During the initiation, phosphine dissociation is a crucial step as the co-ordination of the olefin species with the ruthenium complex is in competition with the re-association of the free phosphine which can lead to deactivation of the catalyst. The formation of the metallocyclobutane (Scheme 1-14) leads to cleavage, producing a new olefinic compound and propagating species **A**. Addition of a second olefin to **A** leads to the formation of a second metallocyclobutane intermediate which releases the desired olefin product **B** and the new catalytic species **C**. The reaction is stopped when there are no alkenes to react with the propagating species, leading to the co-ordination of free phosphine and the deactivation of ruthenium complex.



Scheme 1-14: Catalytic cycle of olefin metathesis.

The general mechanistic pathway of olefin metathesis reaction is always the same, however the difference in the selection of the ligands considerably influences the stability and activity of the initiators.

L-type ligand: A large increase in activity is observed when L is changed from a phosphine to an *N*-heterocyclic carbene due to their differing electronic properties.[32] The electron-donating ability of the *N*-heterocyclic carbene stabilizes the propagating complex and accelerates the oxidative addition required for metallacyclobutane formation before the phosphine ligands can re-associate to the propagating species. In the most efficient catalysts, the increasing σ-donor ability of L facilitates the dissociation of PR_3 and destabilizes the intermediate complex making the olefin insertion more favourable.[34]

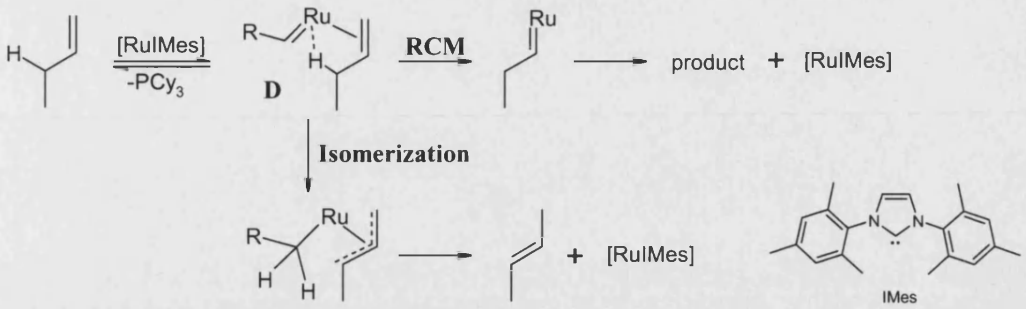
Phosphine-type ligand (PR_3): As stated previously, the major pathway was found to involve phosphine dissociation from the metal centre. A minor associative pathway, in

which both phosphines remain, can be considered to operate only at high phosphine concentration (when excess phosphine is added to the reaction). Large and electron-donating phosphines increase the activity of the catalysts following the order determined by Grubbs and co-workers: $PR_3 = PPh_3 < P^iPr_2Ph < PCy_2Ph < P^iPr_3 < PCy_3$. Bulkier phosphines favour phosphine dissociation by relief of steric crowding around the ruthenium centre and stabilize the Ru(IV) metallacyclobutane intermediate.[29]

Halogen-type ligand (X): Halogens which are small and electron-withdrawing, increase the activity of the catalysts following the order determined by Grubbs and co-workers: X = I < Br < Cl. The size of the halogen could also affect the equilibrium for olefin binding which binds *cis* to one of the halogens, therefore we expect that larger halogens such as iodide would disfavour olefin binding due to steric crowding within the olefin complex. Because the olefin binds *trans* to the other halogen ligand, more electron-withdrawing halogens with a smaller *trans* influence will destabilize the ruthenium-olefin complex.[29]

Alkyl-type ligand (R′): The ligand R′ also has a large influence on the initiation rates of these catalysts, with sterically bulky and electron-donating groups (eg. alkyl) leading to higher initiation rates because they more effectively promote phosphine dissociation. In contrast, small and electronically neutral groups (eg. H) are less effective at labilizing the phosphine ligand.[32]

The study of olefin metathesis catalysts, when used with substrates requiring high temperature and long reaction times, showed an occurrence of both olefin metathesis and olefin isomerisation.[35] The isomerisation can result from decomposition products from the Ru catalyst and has only been noticed with substrates which react slowly by RCM or at high temperature, these conditions being necessary to overcome the high energy of activation of isomerisation. Mechanistically, the ruthenium first coordinates to the less sterically crowded olefin with the allylic proton from the second olefin being trapped by the carbene carbon. The high oxidation state of the Ru in complex [RuIMes] generally disfavours the formation of the hydride complex (Scheme 1-15):



Scheme 1-15: Mechanism leading to isomerisation.

The solvent selection proved crucial in influencing the product distribution of the reaction due to its coordination ability. The more coordinating the solvent, the more it will prevent the second double bond from coordinating to the Ru centre, which is necessary to achieve the RCM process, so isomerisation will be favoured. In the case of dienes leading to "easy" RCM (which do not need a high temperature or an extended reaction time), the coordination to the second double bond will be rapid enough to avoid the slower isomerisation process. The use of an additive such as tricyclohexylphosphine oxide which is a very weakly binding and bulky ligand, proved to be highly efficient in inhibiting isomerisation. It is able to coordinate to the intermediate complex **D**, preventing proton abstraction and π-allyl formation, or by hindering the interaction, but weakly enough not to affect the metallacyclobutane formation and the RCM process.

1.2 Olefin metathesis catalysts

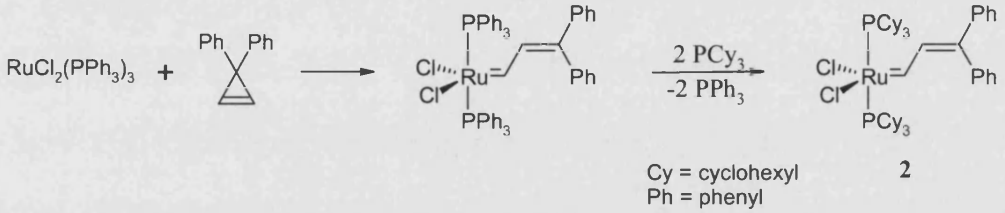
There are a large number of metal carbene complexes used as catalysts in olefin metathesis reactions. Molybdenum and ruthenium systems (Figure 1-2) have been more frequently used for this application[11] than titanium or tungsten initiators due to their greater efficiency. However, until recently, one major constraint of particular interest was the instability of the first generation catalysts.

1.2.1 Development of ruthenium-based olefin metathesis catalysts

In 1992, Grubbs synthesised a new single-component ruthenium-based olefin metathesis catalyst (Ru-benzylidene carbene complex) **2**.[36] This had a significantly lower activity than Schrock's molybdenum complex **1**, but an improved version was synthesised and is now commonly called 'Grubbs catalyst' **3**. It has drawn a lot of attention because it is easy to handle, highly active and relatively stable in air and in the presence of water, but most significantly, it is tolerant towards many different organic

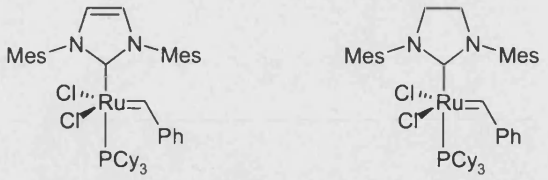
functional groups such as amides, ketones, aldehydes, acids, ethers and alcohols. Ruthenium phosphine based catalysts **2** and **3** have been used successfully in the synthesis of numerous compounds using ring-opening metathesis polymerisation, ring-closing metathesis and acyclic cross metathesis.

Ruthenium vinylidene **2** can be easily obtained by reaction of $RuCl_2(PPh_3)_3$ with 3,3-diphenylcyclopropene followed by ligand exchange with PCy_3 (Scheme 1-16),[37,38] while ruthenium benzylidene complex **3** was obtained using phenyldiazomethane instead of cyclopropene.[39]



Scheme 1-16: Synthesis of Ruthenium complex **2**.

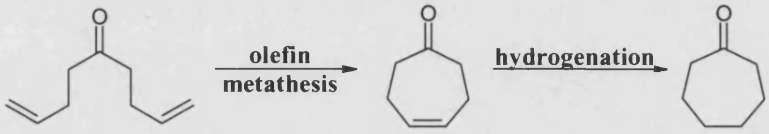
Despite being stable to air and water, the efficiency of Grubbs first generation ruthenium-based catalyst was never comparable to molybdenum complex **1**. Grubbs' group developed a more efficient ruthenium-based catalyst **6** (Figure 1-4) by exchanging one of the tricyclohexylphosphine ligands with an *N*-heterocyclic carbene, imidazolinylidene ligand (IMes) forming the so called "second generation Grubbs catalyst".[40] As previously explained (1.1.3 Mechanism), *N*-heterocyclic carbenes used as ligands are more electron-donating than phosphines, stabilising the propagating complex **C** (Scheme 1-14), and accelerating the oxidative addition before the phosphine re-associates to the propagating species. The reactivity of these catalysts are comparable to the molybdenum complex **1**, when tested in ring-closing metathesis, and gave better results than phosphine-based catalyst **3**, especially with di-, tri- and *tetra*-substituted alkenes. Imidazolylidene-based catalyst **6** has been used in the synthesis of macrocyclic ethers and its stereoselectivity and stability proved to be comparable to benzylidene catalyst **3**. A saturated analogue of imidazolylidene based catalyst **6** was synthesised by exchanging one of the tricyclohexylphosphine ligands from ruthenium-based catalyst **3** with a saturated imidazolinylidene ligand (SIMes) **7**.[41-44] Both second generation catalysts **6** and **7** are highly stable catalysts and have a longer half-life in solution compared to the first generation catalyst (complex **7** is now commercially available).



6 7

Figure 1-4: Second generation imidazolylidene-based Grubbs catalysts **6** and **7**.

Grubbs and co-workers have shown the efficiency of first and second generation ruthenium-based catalysts **3** and **7** when used as pre-catalysts for mediating olefin metathesis and hydrogenation reactions (Scheme 1-17). These two reactions can be performed in tandem to give well-defined co-polymers[45] using both complexes **3** or **7** which are also efficient in different catalytic hydrogenations, including regiospecific ketone and olefin reductions, transfer hydrogenation of ketones and dehydrogenation oxidation of alcohols.

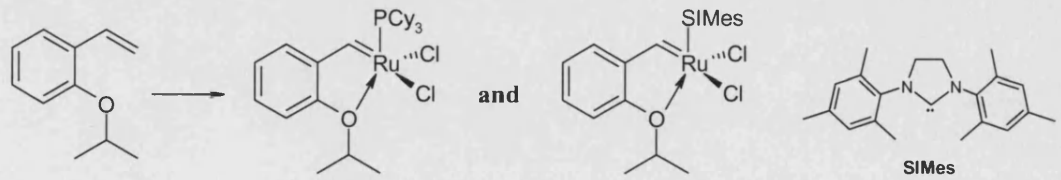


Scheme 1-17: Tandem ring-closing metathesis-hydrogenation catalyzed by first and second generation benzylidene catalysts **3** or **7**.

A range of new initiators, based on second generation Grubbs catalysts were synthesised,[46] establishing new routes towards the ruthenium alkylidene complex.

1.2.2 Improvement of stability of ruthenium-based catalysts

In the course of their study of olefin metathesis, Hoveyda and co-workers observed a decrease in the efficiency of Grubbs first-generation catalyst in the presence of 1-*iso*-propoxy-2-vinylbenzene **8** (Scheme 1-18) in a ring-opening metathesis polymerization reaction.[47] The chelation between the ethereal oxygen and the metal gives extra stability to the ruthenium complex **9**, decreasing its sensitivity to air and moisture, improving its efficiency.



8 9 10

Scheme 1-18: Hoveyda's catalysts when first **9** or second generation **10** Grubbs catalysts are used.

Methyl, ethyl and *iso*-propyl groups were compared for their effect on the stability of the complex, with the *iso*-propyl compound showing the best results in ring-closing metathesis. The second generation Ru-chelate complex **10**[48] was produced and proved to be more robust than Hoveyda's first generation ruthenium-based complex **9** due to its ability to stabilize the propagating species **C** (Scheme 1-14) and to accelerate the oxidative addition when used in olefin metathesis reactions. Second generation complex **10** has no phosphine ligand, and therefore initiation is achieved by the loss of O-Ru chelation. This has the additional advantage that the phosphine cannot inhibit the reaction by re-association to the methylidene active species **C** (Scheme 1-14). These compounds can be recovered and purified by flash chromatography and reused in subsequent reactions.

A series of new molybdenum and tungsten complexes, such as **11**[49] and **12**[46,50,51] (Figure 1-5) was synthesised with the aim of optimising the enantioselectivity of the catalysts in ring-closing metathesis.

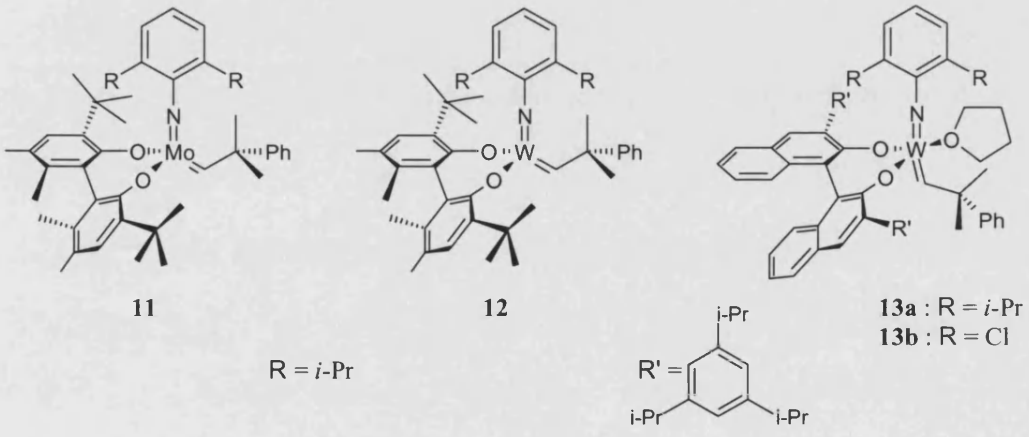
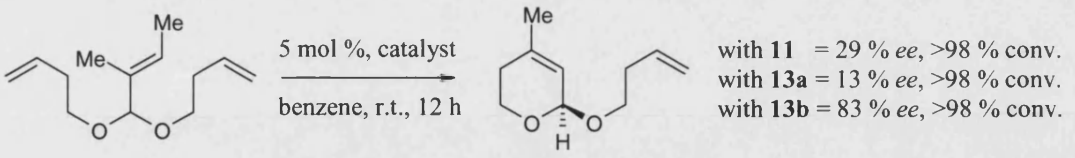


Figure 1-5: Enantioselective molybdenum and tungsten complexes.

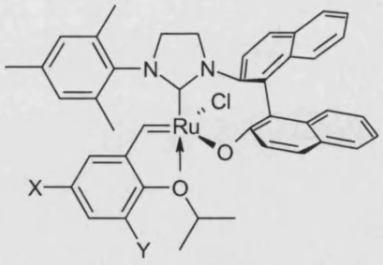
For example, several analogues of binaphthyl molybdenum complex **13a** and **13b** were synthesised and tested in the ring-closing metathesis of acetal compound **14**[52] and complex **13b** was found to give better selectivity than biphenyl molybdenum complex **11** (Scheme 1-19).



14 15

Scheme 1-19: Comparison of enantioselectivity of molybdenum complexes in the ring-closing metathesis of acetal **14**.

The development of such complexes was used in the enantioselective synthesis of a series of compounds[52-54] and helped the improvement of ruthenium-based catalysts. In 2002, second generation binaphthyl initiator **16**[55] (Figure 1-6) was developed and showed high reactivity in asymmetric olefin metathesis reactions. However, complex **16** proved to be less reactive than second generation complex **10** probably due to steric (large chiral ligand) and electronic factors (replacement of Cl by an aryloxy group). By adding substituents onto the benzylidene and binaphthyl moieties, Hoveyda hoped to enhance its activity through electronic and steric changes.[56] For example, adding an electron-withdrawing nitro group *para* to the *O-i*Pr on the benzylidene ligand **16a** (position X, Figure 1-6) weakens the chelated *i*Pr*O*-Ru bond, facilitating initiation of the catalytic cycle. The most efficient analogue **16b** promotes asymmetric olefin metathesis reactions 100 times faster than binaphthyl ruthenium complex **16**. This increase in activity is due to the release of the sterically demanding phenyl-substituted benzylidene *ortho* to the *O-i*Pr which appears to restrict the space available to the adjacent *O-i*Pr.



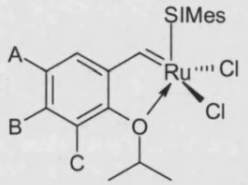
16 X = Y = H
16a X = NO_2, Y = H
16b X = H, Y = Ph

Figure 1-6: Non-phosphine Ruthenium-based chiral metathesis catalyst **16**.

1.2.3 Optimisation of catalytic activity of ruthenium-based catalysts

At a similar time, a route towards second generation complex **10** was developed that first linked the alkylidene ligand followed by the saturated imidazolylidene ligand (SIMes) to form Hoveyda's second generation catalyst **10**.[57] Later analogues of this

initiator were produced by adding substituents at various positions on the phenyl moiety (Figure 1-7) and were tested for reactivity in ring-closing metathesis.[58] These substituents changed the electronic effect of the alkylidene ligands on the ruthenium (see chiral binaphthyl ruthenium catalyst **16** and analogues (Figure1-6)), with the substituted phenyl ruthenium complexes (**17** and **18**) (Figure 1-7) showing a better reactivity in ring-closing metathesis than the initial catalyst **10**. This increased activity is generated by electron-withdrawing of the substituents, creating a faster release of the phenyl ligands and consequently of the active species.

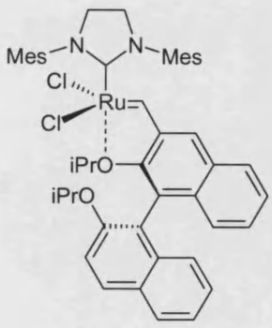


A, B, C = H, O*i*Pr, Me, F, CF_3 or CN

10 A = H, B = H, C = H
17 A = H, B = H, C = F
18 A = H, B = CN, C = H

Figure 1-7: Blechert's analogues of **10**.

Blechert's group also developed catalysts synthesised from 2,2'-dihydroxy-1,1'-binaphthyl (binol)[59] **19** (Figure 1-16) and from biphenyl **20**, which were able to quickly ring-close substrates (even substituted alkenes) that were unreactive to first generation Grubbs catalyst **3**.[60,61] As for binaphthyl ruthenium complex **16** (Figure 1-6), the increase in the steric bulk improved the leaving group ability of the ligand, thus facilitating formation of the catalytically active 14-electron species **C** (Scheme 1-14), and suppressing re-association to the metal centre, which deactivates the catalyst. A kinetic study of ring-closing metathesis of a tosylated protected dipropenylamine, comparing these two new catalysts to second generation Grubbs catalysts **7** showed the superiority of these new analogues in contrast with catalyst **7**.



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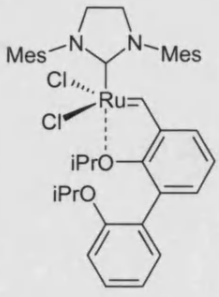

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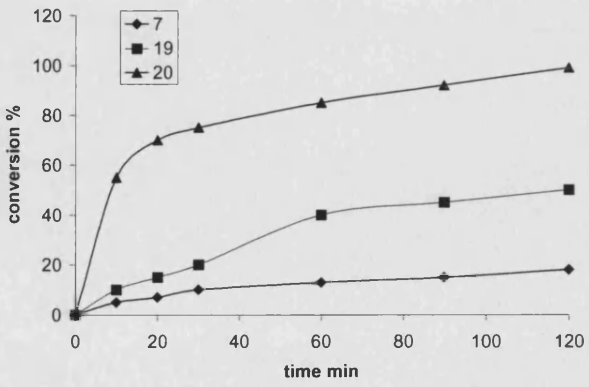
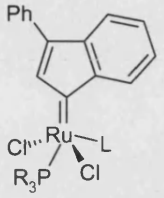


Figure 1-8: Kinetic study of Blechert's binol and biphenyl supported catalyst **19** and **20** in ring-closing metathesis: tosylated diprop-2-enylamine, dichloromethane, 1 mol % catalyst (**7**, **19** or **20**), 0 °C.

1.2.4 Other ruthenium-based catalysts

A series of ruthenium complexes based on indenylidene (**21-23**, Figure 1-9) were produced and tested in ring-closing olefin metathesis,[62] showing that altering the ligand (L) varies their reactivity with different substrates (1.1.3 Mechanism). Second generation ruthenium-based complex **23** showed the best efficiency when used at room temperature in ring-closing metathesis.

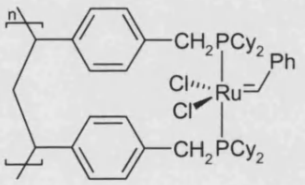


L = PPh_3, **21**
L = PCy_3, **22**
L = IMes, **23**

Figure 1-9: Nolan's indenylidene ruthenium complexes.

1.3 Polymer-supported catalysts

Ever since the introduction of the first polymer-supported ruthenium initiator **24**[63] (Figure 1-10) by Grubbs and co-workers, a number of researchers[64-74] have tried to improve olefin metathesis catalysts by attaching them to a wide range of solid supports. This helps to both decrease any metal contamination in reaction products and adds the recyclability to the efficiency and stability of existing catalysts.



Cy = cyclohexyl

24

Figure 1-10: The first solid-supported initiator developed by Grubbs.

1.3.1 Precursor of solid-supported catalysts: "Boomerang catalyst"

In the late 1990s, it was determined that the main failings of Schrock's molybdenum catalyst **1** and first generation ruthenium Grubbs catalysts **3** were poor recyclability and contamination of the product mixture with coloured metal residue that had to be removed by column chromatography. Barrett's group decided to attach Grubbs first generation catalyst to a polystyrene resin that would act as a support and add recyclability to the already efficient catalyst. The resulting "polymer-supported catalyst"

25 (Figure 1-11) was isolated as orange-brown beads and, once dried, the resin was found to be a long-lived air-stable catalyst. Subsequently, the second generation Ru complex **26** was developed giving a more efficient polymer-supported catalyst.

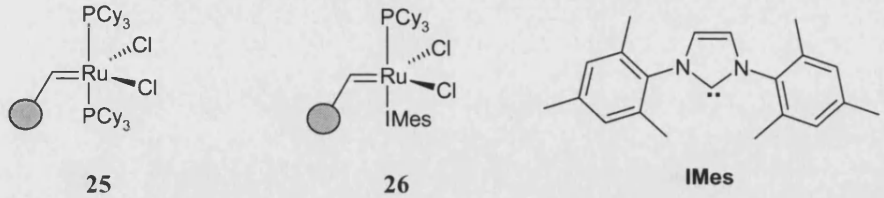
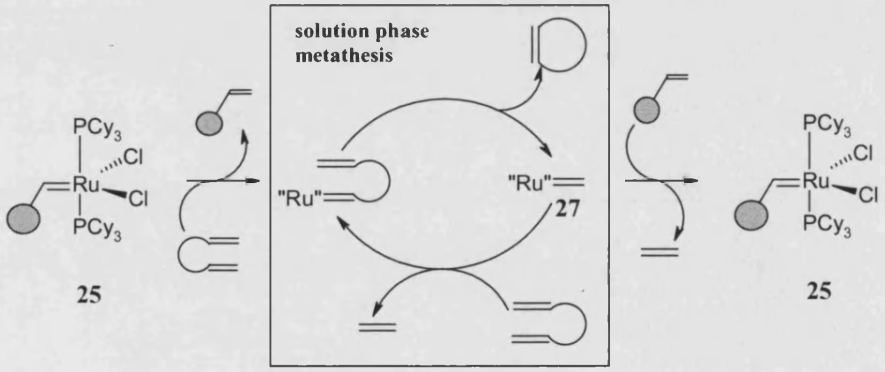


Figure 1-11: Barrett's polymer-supported catalysts.

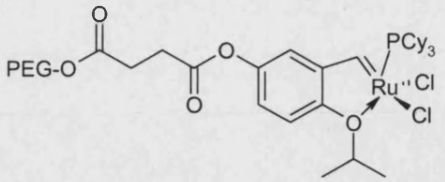
When used in olefin metathesis the initiator becomes homogeneous in solution and methylidene intermediate **27** is then recaptured by the polymer (Scheme 1-20) limiting the amount of residual catalyst in the reaction mixture. This new generation of catalysts was named "boomerang catalysts"[75,76] and showed good recyclability but still required an inert atmosphere and the addition of an alkene to prevent decomposition of the polymer-supported catalyst **25** to be truly recyclable.



Scheme 1-20: "Boomerang" catalytic cycle.

1.3.2 Ligand supported on a solid adding recyclability to ruthenium-based catalysts

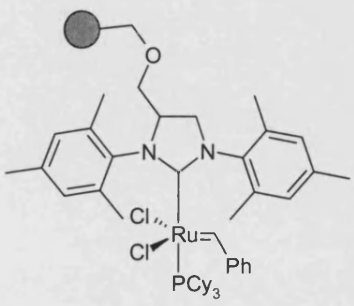
Yao *et al.* decided to use the extra stability of Hoveyda's catalyst **9** to create a polymer-supported catalyst[74] (**28**, Figure 1-12) by attaching it to poly(ethylene glycol) mono-methyl ether, a soluble polymer allowing homogeneous catalysis. This new catalyst proved to have a high recyclability as it still showed high reactivity after eight uses (> 90 %).



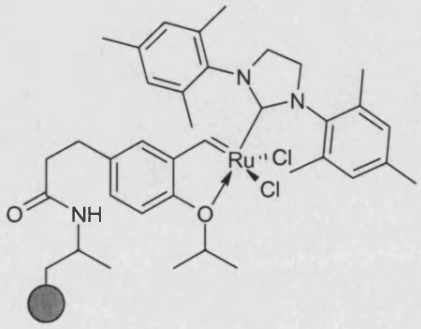
28

Figure 1-12: Yao's poly(ethylene glycol)-suppored ruthenium-based catalyst **28**.

Second generation Grubbs catalysts **6** and **7** (carrying IMes and SIMes ligands respectively) are robust, highly reactive air/water stable catalysts. Unfortunately, due to their homogeneity, they face the same problems as molybdenum based catalyst **1** and ruthenium-based catalyst **3**. In olefin metathesis reactions, residues of ruthenium are left, leading to isomerisation and an increase in the toxicity of the final material. Blechert limited the quantities of ruthenium residues by immobilizing the catalyst on a solid support thereby allowing separation from the products by simple filtration. This method differed from Barrett's "boomerang catalyst" in that it did not require the addition of an alkene because the solid support was directly attached to the *N*-heterocycle carbene (NHC) ligand. Following dissociation of the phosphine ligand during the initiation of the olefin metathesis reaction, the *N*-heterocycle carbene remains attached to the ruthenium centre because NHCs are stronger Lewis bases than phosphines. In an extension of this work, the 4,5-dihydroimidazolinylidene (SIMes) derivative was produced because of its higher Lewis basicity, giving the permanently immobilized and highly active olefin metathesis catalyst **29** (Figure 1-13) after attachment of a solid support (Merrifield-polystyrene) to the *N*-heterocycle carbene ligand of **7**.[77,78] The only problem is that, as the solid support stays attached to the active species during the olefin metathesis reaction, the reaction does not occur in homogeneous conditions which limits the conversions.



29

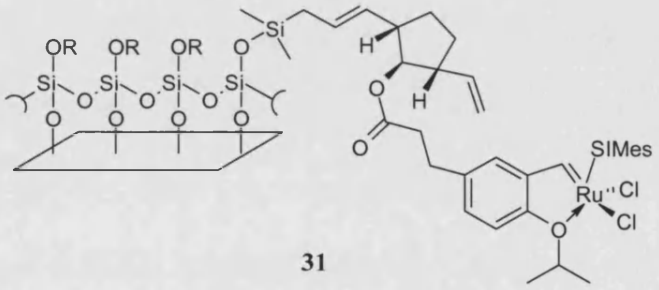


30

Figure 1-13: Blechert polymer-supported catalysts.

In an attempt to resolve the problem of ring-closing and cross metathesis in protic solvents such as methanol and water, a modified second generation catalyst **10** was developed. Immobilization of this analogue on hydrophilic amino methyl PEGA resin which was previously proven to be stable under olefin metathesis conditions, produced PEGA-supported catalyst **30** (Figure 1-13).[79] The hypothesis was that the reaction would occur in the resin pores where the concentration of the active species is high, allowing an improved exposure of the substrate to the hydrophobic ruthenium moiety. Ruthenium *iso*-propylphenyl supported initiators **10** and **30** were compared in ring-closing metathesis reactions using non-degassed solvents under atmospheric conditions, with supported catalyst **30** showing a good reactivity in water. Attachment of a water-insoluble ruthenium alkyl moiety onto a hydrophilic support produced catalysts that are efficient in olefin metathesis in protic solvents with certain substrates.

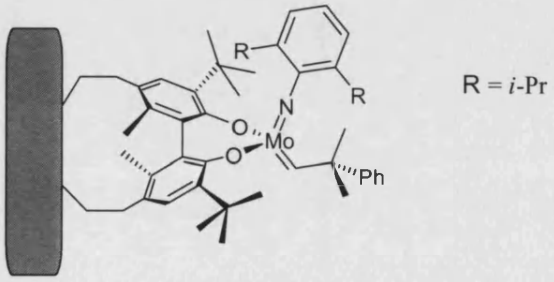
A range of solid supports have been explored including an immobilisation on monolithic sol-gel which provides an efficient, recyclable and practical catalyst **31** (Figure 1-14).[67]



31

Figure 1-14: Sol-Gel supported catalyst **31** for organic and combinatorial synthesis.

The enantioselective molybdenum catalyst **11** (Figure 1-5) was also attached to a polymer support[72] and the resulting complex **32** (Figure 1-15) proved to be as useful as the homogeneous analogues, giving high enantioselectivity (> 90 %).



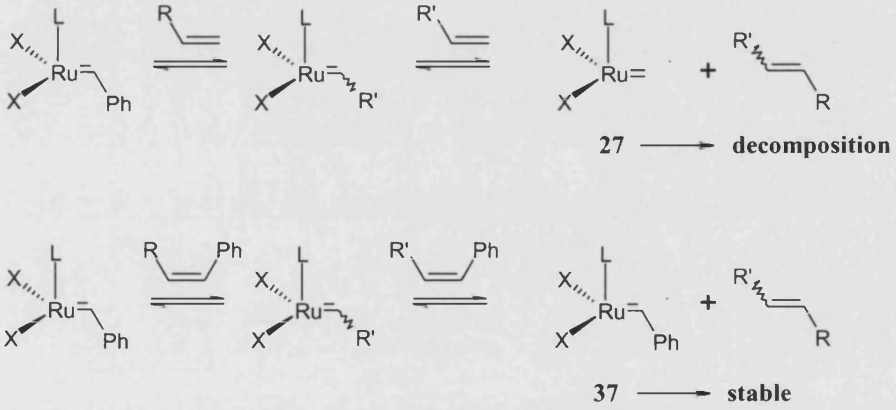
32

Figure 1-15: Chiral molybdenum catalyst for enantioselective olefin metathesis reactions.

1.4 Olefin metathesis catalysts in water

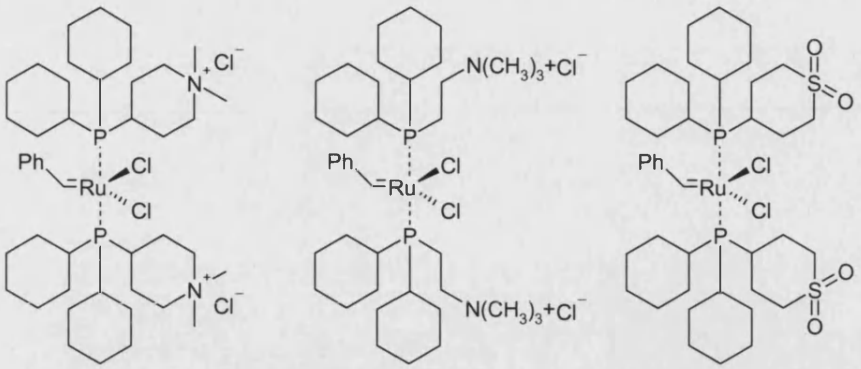
1.4.1 Water-soluble catalysts

Grubbs and co-workers developed new olefin metathesis catalysts **33** and **34** (Figure 1-16) bearing water-soluble aliphatic phosphines that were designed to maintain the tricyclohexyl phosphine and thus preserve the steric and ideal electronic properties that lead to stable and active catalysts. Installation of quaternary amine functionality into tricyclohexyl phosphines provides catalysts that are highly soluble in polar solvents and stable in methanolic solution for weeks or in water for a few days.[80,81] These catalysts were successfully used for ring-opening metathesis polymerization in polar solvents, methanol and aqueous emulsions, initiating rapid and quantitative results. However, ring-closing metathesis in the same solvents failed to convert α,ω-dienes because of the instability of the methylidene intermediate **27** (Scheme 1-21) which rapidly decomposes. This problem was partially solved by introducing a substituent (methyl or phenyl) to the alkene moiety, leading to a more stable alkylidene intermediate and quantitative cyclization.[82,83]



Scheme 1-21: Secondary reaction in water.

This suggests that substrates containing terminal or internal olefins would successfully undergo ring-closing metathesis.[83] Another methanol/water-soluble complex for olefin metathesis **35** (Figure 1-16) [84,85] was developed featuring sulfones on one of the tricyclohexyl moiety which are similar to the quaternary amines of complexes **33** and **34**.



33 34 35

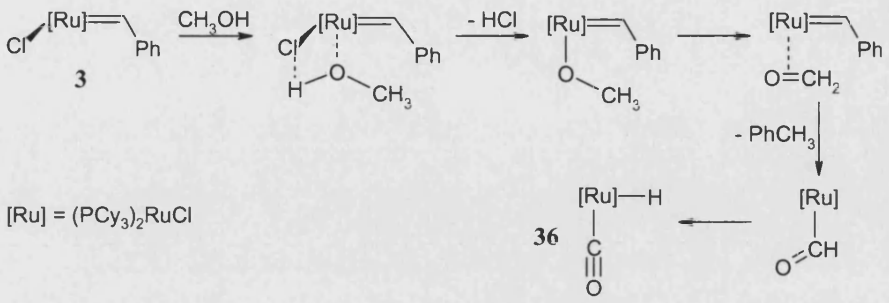
Figure 1-16: Grubbs methanol/water-soluble ruthenium catalysts.

1.4.2 Degradation of olefin metathesis catalysts

In the late 1990s, Grubbs and co-workers studied the decomposition and longevity of several ruthenium carbene-based olefin metathesis initiators. As already discussed, Grubbs catalyst **3** is used to initiate the olefin metathesis reaction, the actual propagating species is the methylidene active species **27** (Scheme 1-21) due to loss of the phenyl after the first turn-over. Methylidene and propylidene were used to study the decomposition and analysis and showed that the methylidene complex **27** has a half life of 40 minutes in deuterated benzene compared to a half life of 8 days for **3**. A significant decomposition pathway for initiator **3** occurs by loss of a phosphine ligand during initiation, followed by the loss of one of the halogens ultimately leading to a hydride complex. It has been shown that these hydrides result in isomerisation reactions as opposed to the required olefin metathesis. The choice of ligands is critical for effective and stable catalytic systems because even minor alterations can have consequences. The utility of a catalyst is determined by the ratio of rate of conversion vs. the rate of decomposition and therefore, ligands that accelerate both processes are not an ideal system.[86]

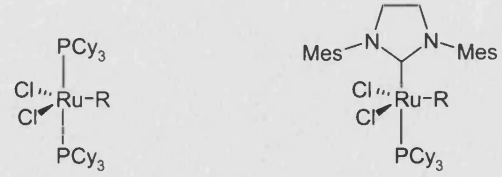
Dinger and Mol specifically studied the degradation of first generation Grubbs catalyst and discovered that when Gubbs catalyst **3** was used with primary alcohols or water, the hydride complex **36** was formed in good yield, especially at elevated temperatures.[87] The pathway pictured in Scheme 1-22 shows the dehydrogenation of the alcohol in addition to the loss of a halogen with subsequent carbonyl ligand formation. Basic conditions seem to facilitate the formation of the hydride complex **36**, a very good

isomerisation catalyst. However, this complex can only be afforded if the solvents used include an oxygen-containing functionality.



Scheme 1-22: Formation of hydride ruthenium complex **36**.

The degradation of second generation Grubbs catalyst **7** with primary alcohols and oxygen was studied in conjunction with the isomerisation and hydrogenation properties of the resulting complexes.[88] When complex **7** was used with primary alcohols such as methanol under basic conditions, the initial brown-pink solution becomes dark orange. NMR analysis of the resulting mixture showed the presence of three different hydrides species, including **37** and **39** (Figure 1-17), in contrast to degradation of first generation Grubbs catalyst **3** which affords only species **37**. The third species cannot be isolated because of its instability. When the alcohol was changed to benzyl alcohol, phenyl species **38** and **40** were afforded in addition to hydride complexes **37** and **39**. Exposure of second generation Grubbs catalyst to oxygen produced phenyl complex **40** as the major product of the reaction. In all the reactions, unexpected diphosphane complexes were formed due to the lability of the N-heterocyclic carbene ligand observed at low temperature.



37 R = H
38 R = Ph

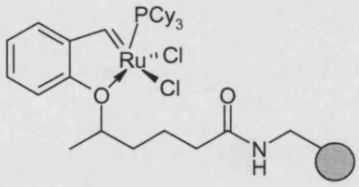
39 R = H
40 R = Ph

Figure 1-17: Degradation hydride complexes.

Phenyl complex **40** is an air-stable solid that proved to be a highly active isomerisation catalyst, considerably more active than first generation complexes **37** and **38**. Second generation phenyl complexes were also shown to be highly efficient hydrogenation catalysts when used at high temperatures, suggesting a possibility for the development of a single-component tandem metathesis-hydrogenation of olefins.

1.5 Development of solid-supported initiator by our group

Our group published the development of an initiator that maintains the stability of Hoveyda's catalyst **10**, is reusable and limits any contamination by ruthenium residues in olefin metathesis reactions. Extending the *iso*-propyl moiety of Hoveyda's catalyst **10** allowed the attachment of a polymer support producing polystyrene-supported ruthenium complex **41** (Figure 1-18).[89] Its reactivity was tested in ring-closing metathesis and despite the conversion not occurring as rapidly as with homogeneous first generation ruthenium-based catalyst **3**, quantitative yields were obtained after a few hours at room temperature, or for shorter times when used under reflux. The recycling of polymer-supported complex **41** was tested with *N,N*-diallylcarbamate and proved to be highly efficient, even after five uses (>60 % conversion), showing the robust nature of the initiator. Experiments have shown that this catalyst does not require an alkene to intercept the unstable methylidene carbene species ($Cl_2(PCy_3)_2Ru{=}CH_2$) **27** (Scheme 1-21) to prevent any decomposition unlike Barrett's boomerang catalyst **25**.



41

Figure 1-18: Dowden's polymer-supported initiator **41**.

1.6 Aims of the project

Olefin metathesis initiators have shown their applicability to the synthesis of a wide range of compounds but have several drawbacks, including the lack of recyclability and the contamination of the product mixture with metal residues that must be removed by column chromatography.

With this in mind, the aim of this project was to design, synthesise and test new, robust, polymer-supported ruthenium alkylidene complexes for olefin metathesis. By extending the *iso*-propyl moiety of Hoveyda's catalyst **10**, we hope to link a solid support such as amino polystyrene and amino PEGA resins to the ligand. This would retain the stability of the initial catalyst while introducing recyclability and ease of use. Our group has previously developed polymer-supported vinyl initiator **41** (Figure 1-18) for olefin metathesis. Initially, the first two steps in the synthesis of initiator **41** proved to be problematic and therefore a new route to improve the synthesis of such a complex is of interest. These solid-supported vinyl initiators will be tested in olefin metathesis reactions using different substrates soluble in both polar and non-polar solvents. The use of a hydrophilic resin may increase the efficiency of our initiators in different types of solvents in order to widen their applications.

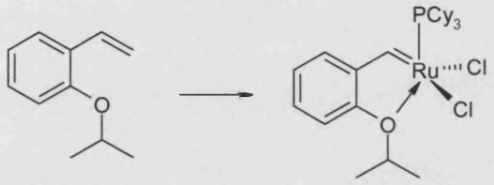
A further aim of the project is to synthesise new ligands with greater stability which will be attached to first generation Grubbs catalyst **3** to form second generation catalysts with higher efficiency in polar solvents. By adding a functional group to the 4,5-dihydroimidazol-2-ylidene ligand (SIMes, Scheme 1-18) we hope to increase the solubility of the catalyst in two ways: when protected, the solubility in organic solvents increases and, when deprotected, the water-solubility of the complex increases.

The development of olefin metathesis initiators that would be efficient in polar solvents could help the creation of chemical probes in the presence of biological target. The final aim of the project was therefore to produce a series of fructose analogues that could be tested for their inhibitory properties towards the fructose transporter GLUT5.

2.0 Improvement of polymer-supported initiator's synthesis

2.1 Previous work

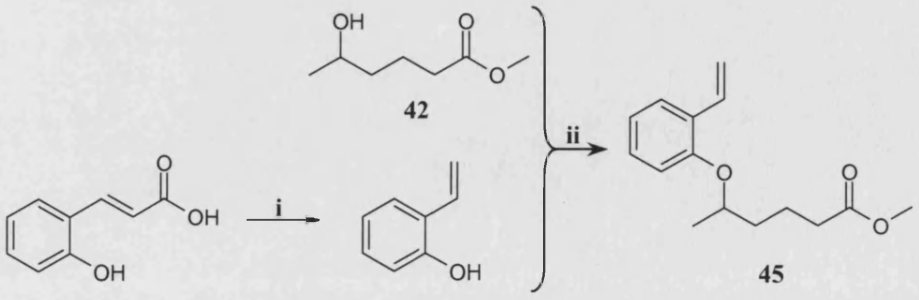
In previous work, our group developed the pre-catalyst **41**[89] (Figure 1-18), through a modification to Hoveyda's initiator **9**[47] (Scheme 2-1). This enabled us to introduce a solid support combining its useful features with the convenience of solid phase methodology. The *iso*-propyl portion, which gives a great stability to the initiator **9**, was extended to accommodate a carboxylic acid group allowing attachment to any solid support. Direct treatment of the ligand with Grubbs catalyst afforded the polymer-supported initiator **41**, which was tested with a range of diene substrates in ring-closing metathesis reactions.



8 **9**

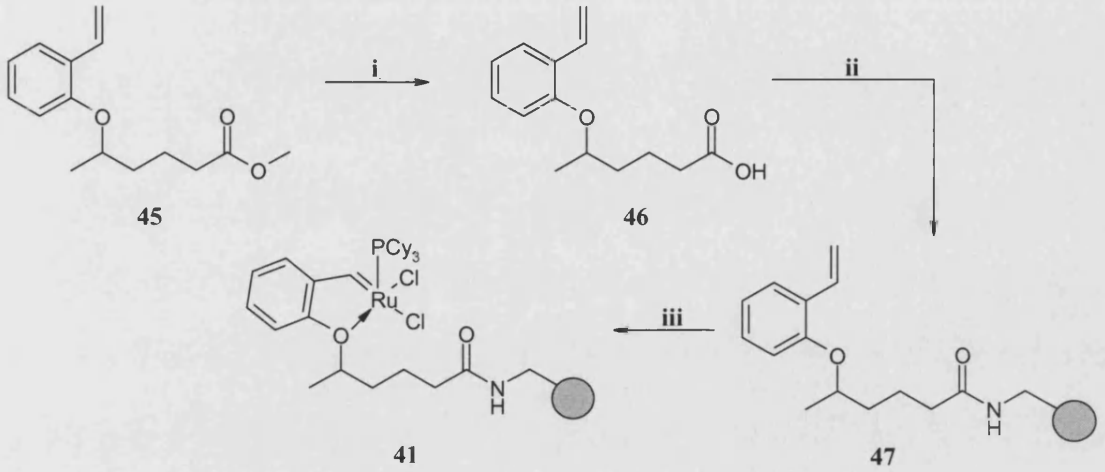
Scheme 2-1: Hoveyda's first generation initiator.

2-Vinylphenol **44** was generated by heating 2-hydroxycinnamic acid **43** at 210°C under vacuum (≤ 1mmHg) in a Kugelröhr apparatus in the presence of 1,4-benzoquinone, which is supposed to prevent polymerisation of 2-vinylphenol.[90] In general, the production of 2-vinylphenol was complicated by polymerisation which resulted in a black solid. The small amount of 2-vinylphenol collected was used crude in a Mitsunobu reaction with alcohol **42** and the resulting product was purified by flash chromatography affording methyl 5-(2-vinylphenoxy)hexanoate **45** as a clear oil, in 8 % yield over two steps for my attempt (Scheme 2-2).



Scheme 2-2: Synthesis of vinyl compound **45**: **i**- benzoquinone, Kugelröhr, 210 °C, 1 mmHg; **ii**- di-*iso*-propyl azodicarboxylate, triphenylphosphine, anhydrous tetrahydrofuran, 0 °C-r.t., 17 h, 8 % (over two steps).

Subsequent hydrolysis using sodium hydroxide released the desired acid **46** to which was added di-*iso*-propylcarbodiimide and 1-hydroxybenzotriazole facilitating the loading onto the aminomethyl polystyrene support (Scheme 2-3). After 15 hours, the resin was washed to afford the polymer-supported ligand **47**, and a small portion of the resin was subjected to the Kaiser test[91] showing no free amine present.



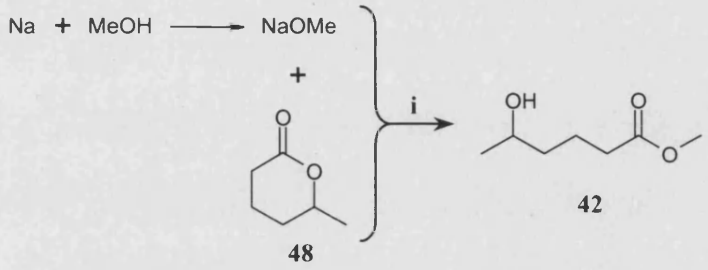
Scheme 2-3: Synthesis of polystyrene-supported initiator **39**: **i**- a) sodium hydroxide (1 M), 1,4-dioxane, r.t., 7 h, b) hydrochloric acid (2 M), 5 min, 91 %; **ii**- di-*iso*-propylcarbodiimide, hydroxybenzotriazole, dichloromethane:dimethylformamide 1:1, r.t., 15 h; **iii**- Grubbs catalyst **3** (5 x 0.1 eq), degassed 1,2-dichloroethane, r.t., 5 x 3 h.

The polystyrene-supported vinyl ligand **47** was then treated 5 times with small portions of Grubbs first generation catalyst in degassed 1,2-dichloroethane, filtered and dried to afford the polymer-supported initiator **41** as brown beads (Scheme 2-3). Unfortunately, the first two steps of the initiator's synthesis proved to be problematic due to polymerisation of the first unstable intermediate (vinyl phenol) and the poor yield of the second step (Mitsunobu reaction). In order to improve the route towards the initiator, vinyl phenol was replaced by the commercially available 2-(prop-1-enyl)phenol and we reasoned that it should be possible to generate the identical initiator after loading with Grubbs first generation catalyst **3**, and liberation of propene.

2.2 Improvement of the synthesis of initiator *via* propenyl route

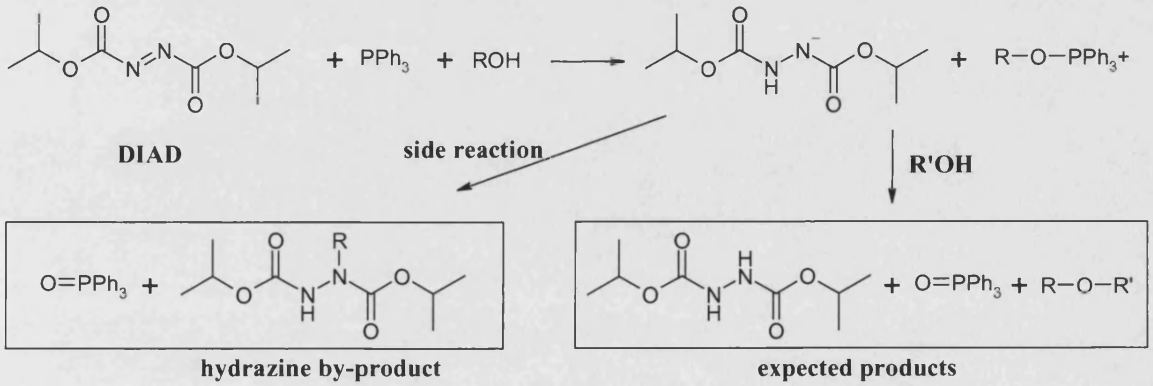
Ring opening of δ-hexanolactone simultaneously provides the secondary alcohol that is important for the stability of the Hoveyda catalyst **9**,[47] as well as a remote methyl protected acid that can be used for the attachment to the solid support.[64] The first goal of the synthesis was to improve the yield of methyl 5-hydroxyhexanoate **42** by using

different methods. For the ring-opening of the lactone, various sources of sodium methoxide including commercially available material were explored. Unfortunately, sodium methoxide can be transformed into sodium carbonate and methanol during storage if it is exposed to atmospheric moisture, reducing its activity. The best method was to use freshly prepared sodium methoxide from sodium and dry methanol[92] (to prevent the formation of sodium hydroxide which inhibits the reaction, preventing it going to completion). The sodium methoxide mixture was thus cannulated at –78 °C into the solution of δ-hexanolactone in anhydrous methanol to afford compound **42** in 94 % yield.



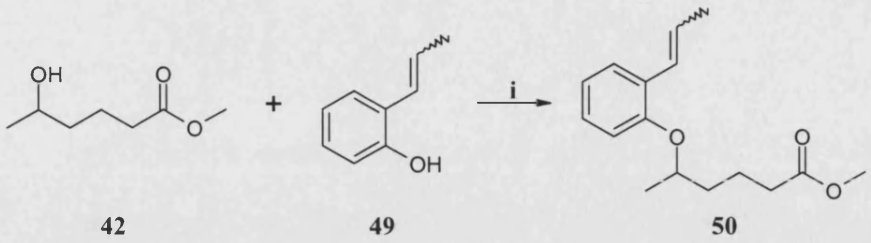
Scheme 2-4: Synthesis of alcohol **42**: **i**- -78 °C, methanol, 4 h, 94 %.

(*E*/*Z*)-2-(Prop-1-enyl)phenol **49** does not suffer from the same stability problems as 2-vinylphenol (initially used in the synthesis of **41**) and is commercially available. However, a Mitsunobu reaction[93] between the phenol and the alcohol initially proceeded in a disappointing 28 % yield. Careful examination of the literature revealed that slow addition of the coupling reagent, di-*iso*-propyl azodicarboxylate, to the remaining reaction mixture avoids the formation of unreactive species such as the hydrazine by-product (Scheme 2-5).



Scheme 2-5: Possible products and by-products from Mitsunobu reaction.

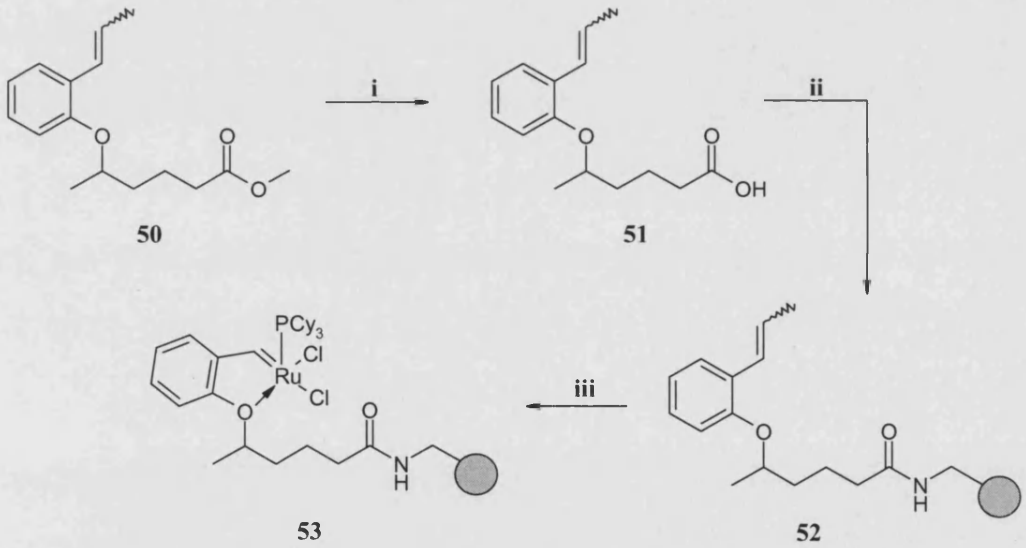
Mitsunobu reaction in tetrahydrofuran using these conditions provided the product **50** in a more satisfying 83 % yield, but this was difficult to reproduce.



42 **49** **50**

Scheme 2-6: Synthesis of ethereal intermediate **50**: **i**- di-*iso*-propyl azodicarboxylate, triphenylphosphine, anhydrous tetrahydrofuran, r.t., 24 h, 83 %.

Subsequent hydrolysis using sodium hydroxide released the desired acid **51** to which was added di-*iso*-propylcarbodiimide and 1-hydroxybenzotriazole facilitating the loading onto the aminomethyl polystyrene support (Scheme 2-7). After 15 hours, the resin was washed to afford the polymer-supported ligand **52**, and a small portion of the resin was subjected to the Kaiser Test[91] showing no free amine present.



50 **51** **53** **52**

Scheme 2-7: Synthesis of polystyrene-supported initiator **53**: **i**- a) sodium hydroxide (1 M), 1,4-dioxane, r.t., 7 h, b) hydrochloric acid (2 M), 5 min, 90 %; **ii**- di-*iso*-propylcarbodiimide, hydroxybenzotriazole, dichloromethane:dimethylformamide 1:1, r.t., 15 h; **iii**- Grubbs catalyst (5 x 0.1 eq), degassed 1,2-dichloroethane, r.t., 5 x 3 h.

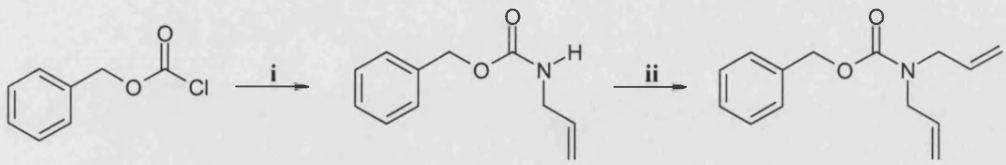
The polystyrene-supported propenyl ligand **52** was treated 5 times with small portions of Grubbs first generation catalyst in degassed 1,2-dichloroethane, filtered and dried to afford the polymer-supported initiator **53** as brown beads (Scheme 2-7).

2.3 Synthesis of olefin metathesis acyclic diene substrates

2.3.1 Organic-soluble substrates

In order to test the solid-supported initiators, different acyclic dienes have been synthesised to undergo ring-closing metathesis to afford 5- or 6-membered rings. Olefin metathesis was performed on substrates containing functional groups such as carbamates, esters, ethers, amines and others. The majority of the substrates synthesised were terminal alkenes although a few substituted alkenes were tested with second generation initiators to determine their ability to catalyse olefin metathesis with this type of substrate. The resulting rates of conversion were initially calculated by analysis of ^{1}H NMR spectra using relative integration (as terminal CH_2 groups are removed during the reaction and the shift of the neighbouring CH= changes).

N,*N*-Di(prop-2-enyl)carbamate **54** was synthesised as our 'standard' reagent, which undergoes ring-closing metathesis in order to obtain benzyl 2,5-dihydropyrrole-1-carboxylate **55**. Benzyl chloroformate **56** was added to allyl amine in dichloromethane at 0 °C and the reaction mixture was stirred for 4 hours at room temperature. Subsequent purification by flash chromatography gave *N*-(prop-2-enyl)carbamate **57** in 67 % yield. Allyl bromide was then added to the prop-2-enyl carbamate compound **57** and the resulting mixture was purified using Kugelröhr distillation to afford benzyl *N*,*N*-di(prop-2-enyl)carbamate **54** in 81 % yield (Scheme 2-8).

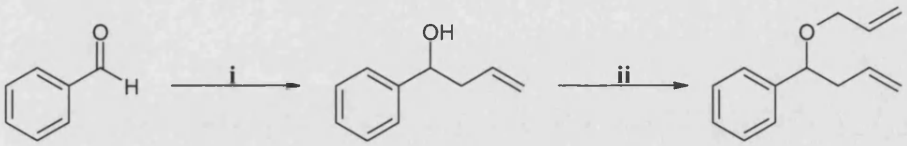


56 **57** **54**

Scheme 2-8: Synthesis of diallyl carbamate substrate **54**: **i**- allyl amine, dichloromethane, 0 °C-r.t., 4 h, 67 %; **ii**- sodium hydride, allyl bromide, dry dimethylformamide, r.t., 20 h, 81 %.

With the aim of producing a six-membered ethereal ring following ring-closing metathesis, (1-(prop-2-enyloxy)but-3-enyl)benzene **58** was synthesised from benzaldehyde **59** in two steps (Scheme 2-9). A Grignard reaction seemed to be the best way to obtain 1-phenyl-but-3-en-1-ol **60** from benzaldehyde **59**, but the high moisture-sensitivity of the reaction affected the production of the desired compound, affording

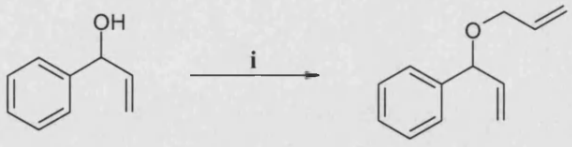
intermediate **60** in a poor yield (18%). The allyl intermediate **60** was finally obtained by addition of allyl bromide to the benzaldehyde **59** compound using bismuth chloride and aluminium.[94] This alternative method is far less water-sensitive compared to the Grignard[95] reaction, the only hazard being that addition of water and tetrahydrofuran to bismuth chloride and aluminium is highly exothermic. The reaction was finally quenched with saturated aqueous ammonium chloride and compound **60** was afforded in 89 % yield. Allyl bromide was then added to the anion of **60** generated using sodium hydride in anhydrous tetrahydrofuran,[96] producing (1-prop-2-enyloxy-but-3-enyl)benzene **58** in 87 % yield.



59 **60** **58**

Scheme 2-9: Synthesis of ethereal diene substrate **58** : **i**- bismuth chloride, aluminium, water-tetrahydrofuran, allyl bromide, r.t., 17 h, 89 %; **ii**- sodium hydride, allyl bromide, anhydrous tetrahydrofuran, 0 °C-r.t., 20 h, 87 %.

A similar diene was synthesised in order to obtain 2-phenyl-2,5-dihydrofuran **61** after ring-closing metathesis. (1-Prop-2-enyloxyprop-2-enyl)benzene **62** was obtained by alkylation of α-vinylbenzyl alcohol[96] **63** under basic conditions in 62 % yield following purification by flash chromatography (Scheme 2-10).

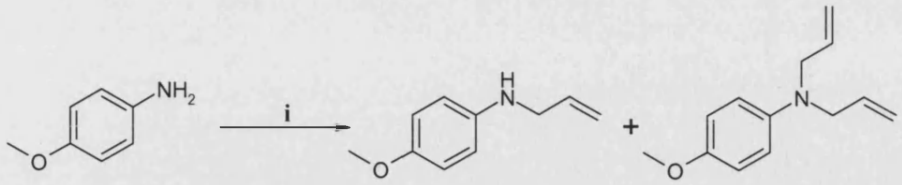


63 **62**

Scheme 2-10: Synthesis of ethereal diene substrate **62**: **i**- sodium hydride, allyl bromide, dry tetrahydrofuran, 0 °C-r.t., 16 h, 62 %.

N,*N*-Di(prop-2-enyl)-4-methoxyphenylamine **64** was prepared by addition of allyl bromide to the sodium anion of 4-methoxyaniline **65** in anhydrous tetrahydrofuran giving a mixture of *N*,*N*-di(prop-2-enyl)-4-methoxyphenylamine **64** and *N*-(prop-2-enyl)-4-methoxyphenylamine **66**. Allylic compounds **64** and **66** were produced in 15 % and 46 % yields respectively (Scheme 2-11), the yield of which could not be improved

by increasing the proportions of the allylic reagent. However, further allylation using the same method, converted the purified mono-allylic compound **66** to the desired diallylic product **64**.

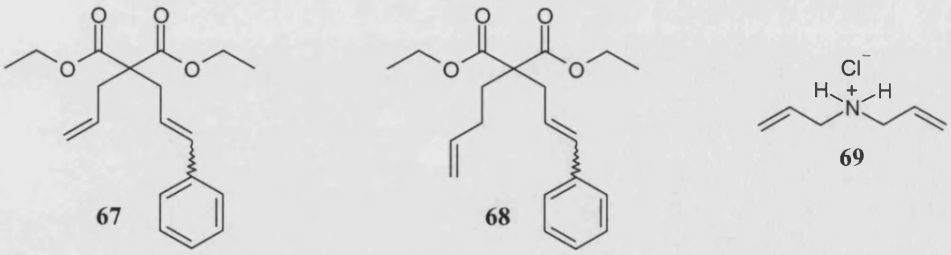


65 **66** **64**

Scheme 2-11: Synthesis of allylamine substrates **64** and **66**: **i**- sodium hydride, allyl bromide, anhydrous tetrahydrofuran, 0 °C-r.t., 20 h, **64** 15 % and **66** 46 %.

2.3.2 Synthesis of methanol/water-soluble substrates

With the aim of testing our solid-supported initiators in non-organic solvents, different methanol/water-soluble substrates[82] were required (**67-69**, Figure 2-1). All the substrates synthesised are acyclic dienes that can undergo ring-closing metathesis reactions to afford 5- or 6-membered rings in the presence of synthetic polymer-supported initiators. As seen in part **1.4.1**, the catalytically active methylene intermediate complex **27** (Scheme 1-21) decomposes prior to complete consumption of the monomer because of its high instability in polar solvents. Addition of a phenyl at the terminal position of the alkene moiety leads, in theory, to higher yields by giving stability to the catalyst by regenerating Grubbs first generation catalyst **3** (or second generation **7** when used with second generation initiator) at every turn over.[7]

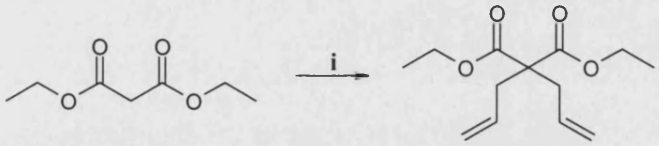


67 **68** **69**

Figure 2-1: Models of water/methanol-soluble substrates.

Malonic substrate **70** was synthesised by treating a cooled solution of diethyl malonate **71** and sodium hydride in tetrahydrofuran with allyl bromide. Flash chromatography revealed that diethyl hepta-1,6-diene-4,4-dicarboxylate **60** was produced (Scheme 2-12)

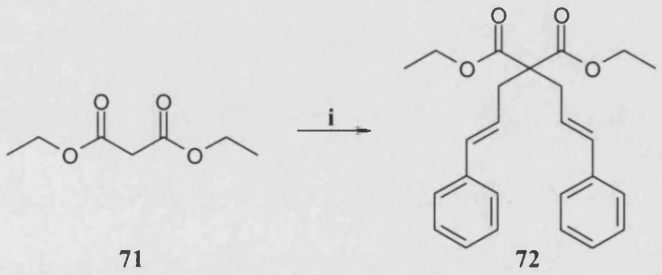
instead of the desired mono substituted 2-prop-2-enyl-malonic acid diethyl ester required for the synthesis of compound **67**.



71 **70**

Scheme 2-12: Synthesis of diene malonic substrate **70**: **i**- sodium hydride, allyl bromide, tetrahydrofuran, 0 °C-r.t., 17 h, 62 %.

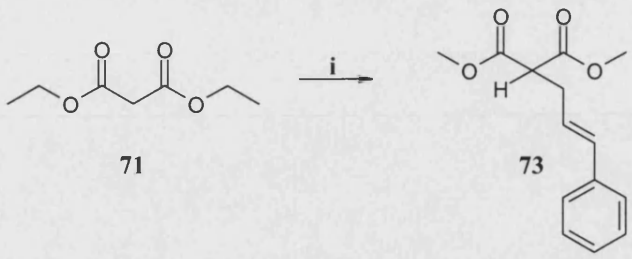
It was thought that by first substituting diethyl malonate **71** with cinnamyl chloride, followed by the more reactive allyl bromide, might produce the desired mono-substituted derivative. Unfortunately using the same technique as previously, cinnamyl chloride substituted twice affording diethyl 1,7-diphenylhepta-1,6-diene-4,4-dicarboxylate **72** in 58 % yield (Scheme 2-13).



71 **72**

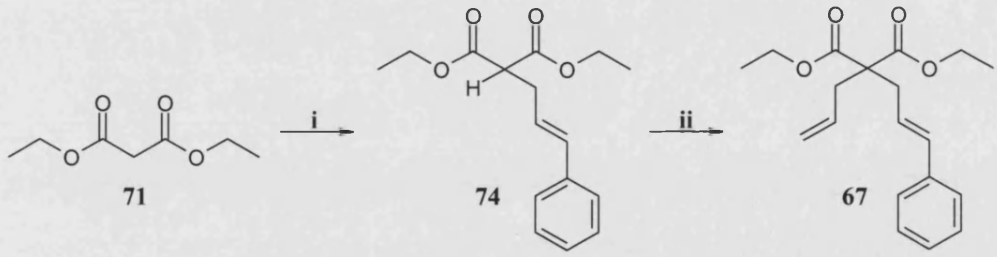
Scheme 2-13: Synthesis of *bis*(phenyl-propenyl) malonic substrate **72**: **i**- sodium hydride, cinnamyl chloride, tetrahydrofuran, 0 °C-r.t., 17 h, 58 %.

It seems that sodium hydride is too strong base for this reaction, as we require mono-deprotonation of the malonate reagent in the α-position of the carbonyl groups. These *bis*-alkylations show that deprotonation occurs twice, therefore a weaker base (sodium methoxide)[97] was sought. This time, treatment of the resulting enolate of diethyl malonate **71** with cinnamyl chloride, furnished the mono-substituted dimethyl (3-phenylprop-2-enyl)malonate **73** in 62 % yield after Kugelröhr distillation (Scheme 2-14).



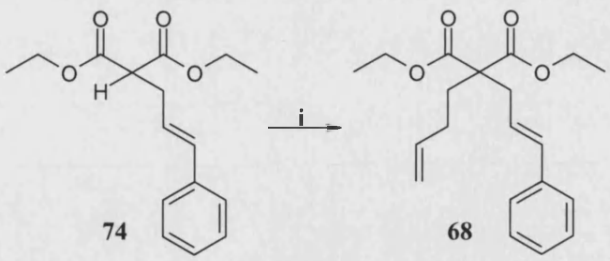
Scheme 2-14: Synthesis of **73**: **i**- sodium methoxide, cinnamyl chloride, methanol, 0 °C-r.t., 18 h, 62 %.

Under these reaction conditions, the expected ethyl ester was not obtained because transesterification also occurred during the alkylation. Ethyl esters of malonate are more frequently used in the literature for ring-closing metathesis which allows us to be able to compare the efficiency of our initiator with literature complexes. To avoid methoxy trans-esterification, a freshly made solution of sodium ethoxide was added to diethyl malonate **71** at 0 °C, allowing ethoxy transesterification which does not affect the structure of the intermediate. Cinnamyl chloride was added after 15 minutes and the reaction mixture was stirred for 17 hours affording diethyl (3-phenylprop-2-enyl)malonate **74** in 61 % yield after purification by Kulgelrohr distillation (Scheme 2-15). Allylation of mono-substituted ester **74** using sodium hydride proceeded smoothly in tetrahydrofuran, furnishing diethyl 1-phenylhepta-1,6-diene-4,4-dicarboxylate **67** in 98 % yield (Scheme 2-15).



Scheme 2-15: Synthesis of 1-phenylhepta-1,6-diene-4,4-dicarboxylate **67**: **i**- sodium ethoxide, cinnamyl chloride, ethanol, 0 °C-r.t., 17 h, 61 %; **ii**- sodium hydride, allyl bromide, tetrahydrofuran, 0 °C-r.t., 6 h, 98 %.

1-phenylocta-1,7-diene-4,4-dicarboxylate **68** can also be synthesised from diethyl (3-phenylprop-2-enyl)malonate **74** by using 4-bromo-1-butene instead of allyl bromide affording substrate **68** in 57 % yield (Scheme 2-16).



74 68

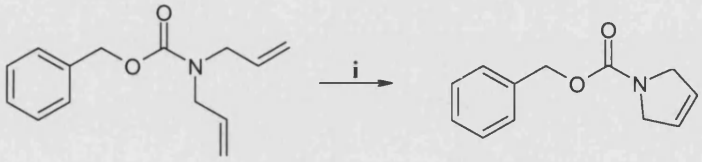
Scheme 2-16: Synthesis of 1-phenylocta-1,7-diene-4,4-dicarboxylate **68**: **i**- sodium hydride, 4-bromo-1-butene, tetrahydrofuran, 45 °C, 17 h, 62 %.

2.4 Testing of propenyl-supported initiators

Polymer-supported propenyl initiator **53** was initially tested for ring-closing metathesis with diallyl carbamate substrate **54** which showed good results when tested with the original initiator **41**.[89] This was deemed an appropriate method to determine whether the reactivity of the propenyl-supported initiator was equivalent to that of the literature vinyl-supported initiator **41** which shows good rates of conversion and recyclability.

2.4.1 Testing with *N,N*-di(prop-2-enyl)carbamate 54

Diallyl carbamate substrate **54** in dichloromethane was added to the polystyrene-supported initiator **53** in a plastic solid phase synthesis tube, which was then sealed and agitated by 360° rotation at room temperature for 3 hours (Scheme 2-17).



54 55

Scheme 2-17: ring-closing metathesis of carbamate substrates **54**: **i**- **53**, dichloromethane, 3 h, r.t..

The rate of conversion of this ring-closing metathesis, determined using relative integration of ^{1}H NMR spectra was 60 %, much poorer than the literature yield of 91% obtained after 90 minutes of rotation when using initiator **41**.[89] As seen previously (Scheme 2-2) the synthesis of polystyrene-supported initiator **53** involves five loadings of first generation Grubbs catalyst (5 x 0.1 eq). In order to establish whether inefficient loadings are the cause of the poor conversion, the resin was loaded a further three times and polymer-supported initiator **53** was tested in ring-closing metathesis with diallyl carbamate substrate **54** after each additional loading (Table 2-1).

Use		1	2	3
Entry	**Load**	**Conversion %[a]**	**Conversion %[a]**	**Conversion %[a]**
1[b]	5	91	81	68
2	5	60	-	-
3	6	72	-	-
4	7	82	-	-
5	8	84	38	22

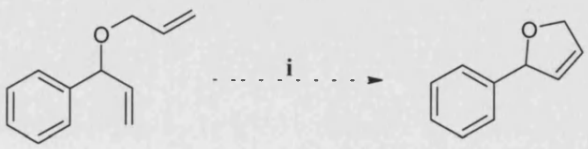
Table 2-1: Rate of conversion of ring-closing metathesis for different loaded polymer-supported initiators; [a] Relative integration of ^{1}H NMR; [b] literature results of ring-closing metathesis using **41**[89].

The rate of conversion was observed to increase with each loading cycle, which can be explained by the increased concentration of Grubbs catalyst complexed to the ligand. Attempts at recycling gave poor yields (entry 5) compared to the results obtained with the original initiator **41** (entry 1) which gave good recyclability even after five uses (63 %).

We therefore sought an improved synthesis of the apparently more efficient vinyl-supported pre-catalyst **41**, in order to provide sufficient material to compare both initiators (propenyl- and vinyl-supported).

2.4.2 Testing with (1-(prop-2-enyloxy)prop-2-enyl)benzene 62

In a plastic solid phase synthesis tube, **62** in dichloromethane was added to the resin-supported initiator **53**. The tube was sealed and agitated by 360° rotation at room temperature for 90 minutes (Scheme 2-18).



62 **61**

Scheme 2-18: Ring-closing metathesis of (1-(prop-2-enyloxy)prop-2-enyl)benzene **62** : **i**- **53**, dichloromethane, 90 min, r.t..

The mixture was then washed with dichloromethane and the resulting organic phase was concentrated and analysed by ^{1}H NMR which showed the presence of dichloromethane, acetone and water, but none of the desired compound. After studying the literature, it was found that the boiling point of 2-phenyl-2,5-dihydrofuran **61** is 104 °C at 15-16 torr and that the compound may have evaporated during concentration. The solution to such a problem was to perform the reaction in deuterated chloroform, filter the reaction mixture and pour it into an NMR tube in order to directly estimate the rate of conversion. This method was used in all cases where a volatile product may be generated by ring-closing metathesis.

2.5 Synthesis of vinyl ligand

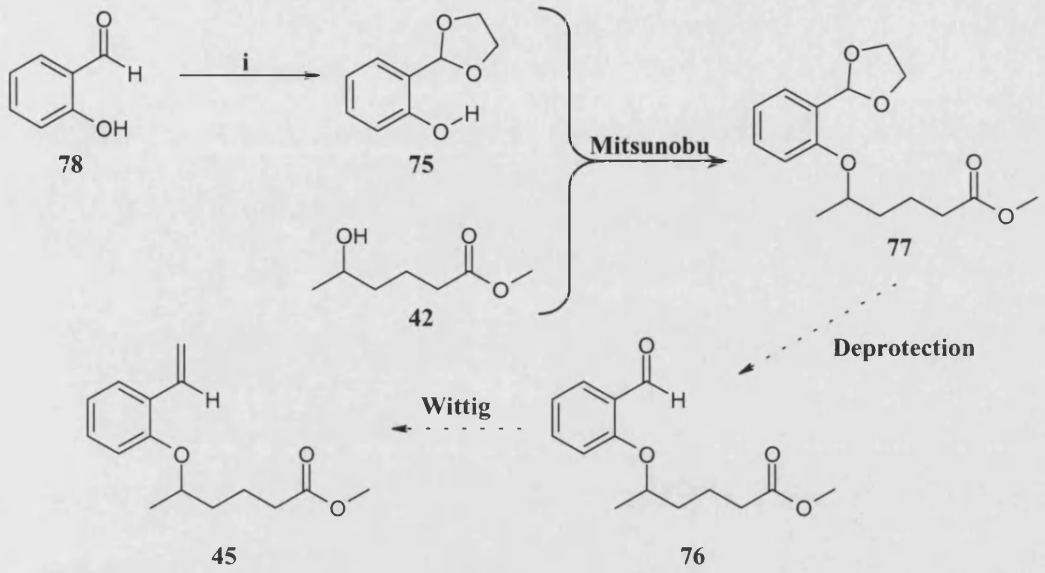
The earlier tests show that the vinyl ligand apparently offers the polystyrene-supported initiator a better efficiency than its propenyl analogue. However, its synthesis proved to be problematic due to the first two steps, leading to a low overall yield. New routes were investigated in order to find an improved synthesis of this efficient initiator.

2.5.1 Synthesis *via* protected aldehyde

As the production of 2-vinylphenol was difficult, other ways to obtain the vinyl ligand were explored. Due to the problem of polymerisation, we sought a different route with the formation of the vinyl moiety occurring at a later stage in the synthesis. Introduction of a protected salicylaldehyde (Scheme 2-19), such as acetal **75** was initially conceived as a reliable route towards aldehyde **76**. Mitsunobu reaction of acetal **75** with alcohol **42** would produce ether **77** which could be used in Wittig reaction[98] after deprotection, providing the vinyl ester **45**. This could be hydrolysed and attached to a solid support and complexed with first generation Grubbs catalyst to afford initiator **41**.

Unfortunately, protection of the salicylaldehyde **78** with ethylene glycol afforded a very unstable compound **75** that could not be adequately isolated (Scheme 2-19). It is likely that the proton from the neighbouring phenol renders the compound very sensitive to moisture, leading to rapid deprotection of the aldehyde. Purification of the acetal **75** was problematic because of the acidity of the silica used for flash chromatography. Consequently, it was distilled using a Kugelröhr at 75 °C under atmospheric pressure. 2-

(2-hydroxyphenyl)-1,3-dioxolane **75** was provided in 21 % yield, but unfortunately the subsequent Mitsunobu reaction was unsuccessful.



Scheme 2-19: Synthesis of methyl 5-(2-vinylphenoxy)hexanoate **45**: **i**- ethylene glycol (2 eq), *para*-toluenesulfonic acid (cat.), toluene, reflux, Dean Stark, 24 h, 21 %.

This route is problematic due to the instability of the protected aldehyde but the idea of using such a functional group that can be converted to a vinyl group at a later stage was highly attractive.

2.5.2 Synthesis *via* alkylation

The problems of a low-yielding Mitsunobu reaction and sensitive acetal **75** encouraged an alternative strategy. Substitution of the alcohol **42** with a good leaving group may be more efficient, therefore a new route involving alkylation of the salicylaldehyde with a bromo analogue of alcohol **42**, was attempted. Substitution of the alcohol functionality by a bromide in compound **42** offers a good leaving group that can then react with the salicylaldehyde (Scheme 2-20).

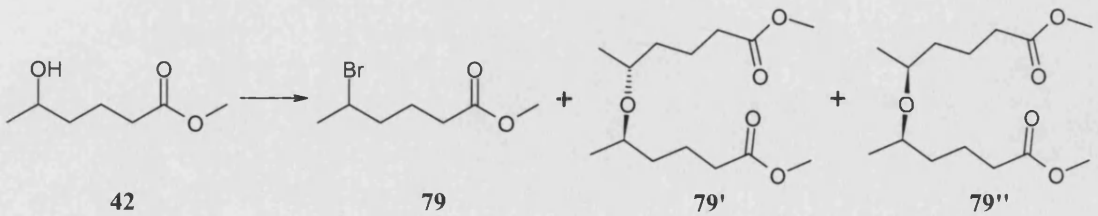
Scheme 2-20: Synthesis of bromo compound **79**: **i**- triphenylphosphine, carbon tetrabromide, pyridine, anhydrous tetrahydrofuran, 2 h, 0 °C-r.t..

Initial attempts at the bromination reaction proved to be somewhat unreliable and some effort was made to examine this reaction. Bromination of the alcohol **42** proved to be an efficient and high-yielding reaction. However, a recent attempt using an identical procedure (Table 2-2, entry 1) gave unsatisfactory yields and has proved to be irreproducible. A number of methods were tested using differing solvents, reaction times and brominating reagents (Table 2-2).

Entry	reaction time	solvent	brominating reagent	yield %
1	17 h	THF	CBr_4	47
2	17 h	$CHCl_3$	CBr_4	21
3	17 h	CH_2Cl_2	PPh_3Br_2	14
4	17 h	CH_2Cl_2	CBr_4	18
5	1 h	CH_2Cl_2	PPh_3Br_2	-
6	2 h	CH_2Cl_2	CBr_4	13

Table 2-2: Results from the bromination reactions.

Some interesting results were observed when using chlorinated solvents such as dichloromethane and chloroform. These reactions afforded a mixture of two compounds that could not be separated by chromatography due to their similar R_f's. ^1H and ^{13}C NMR suggest that these compounds are an isomeric mixture of dimers (**79'** and **79''**, Scheme 2-21). This was observed more often in chlorinated solvents than in tetrahydrofuran, but it was noted that longer times produced more secondary products in this solvent.

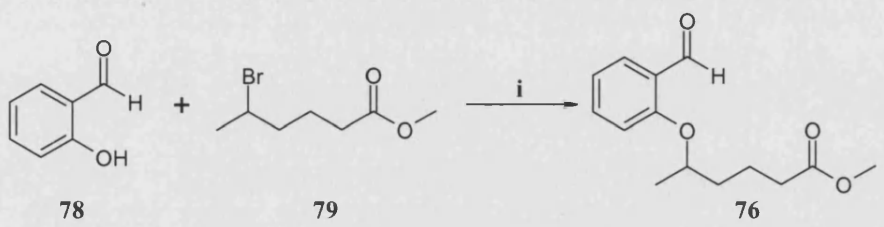


42 **79** **79'** **79''**

Scheme 2-21: Bromination of methyl 5-hydroxy-hexanoate **42**.

Production of bromide **79** was achieved in 84 % yield by treatment of a cooled solution of alcohol **42** in tetrahydrofuran with triphenylphosphine, pyridine and carbon tetrabromide and stirring for two hours.[99]

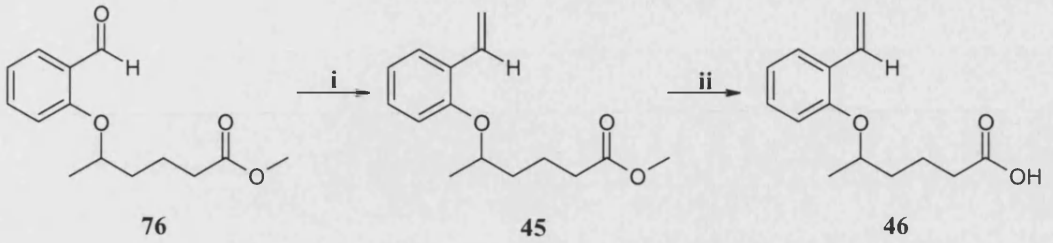
In light of the problems in producing protected salicylaldehyde **75**, direct alkylation of salicylaldehyde **78** was attempted (Scheme 2-22). Indeed, *in-situ* formation of the potassium salt of salicyladehyde using potassium carbonate in dimethylformamide, followed by addition of the bromo-compound **79** by cannula transfer afforded a good yield of 5-(formylphenoxy)hexanoate **76** (72 %). The use of different solvents such as *N*-methylpyrrolidone (NMP) did not increase the yield of the reaction, while the presence of moisture in the reaction did not seem to affect it.



78 **79** **76**

Scheme 2-22: Synthesis of ethereal compound **76**: **i**- potassium carbonate, anhydrous dimethylformamide, 17 h, r.t., 72 %.

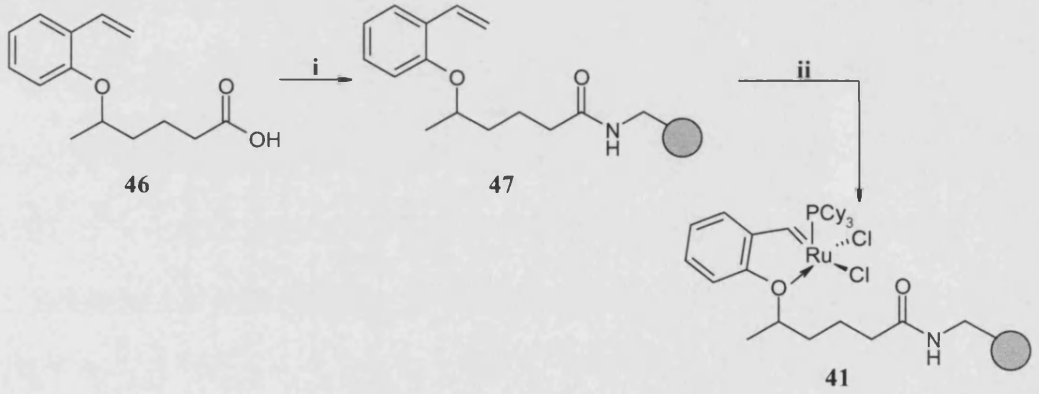
The next step was a Wittig[98] reaction to convert the aldehyde functionality to a vinyl, which, by subsequent hydrolysis, would afford acid **46** (Scheme 2-23). Three different Wittig methods were tested in order to optimise the reaction. Methyltriphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran were heated at reflux for 50 minutes and then cooled to room temperature. [100] After addition of the aldehyde **76**, the reaction mixture was heated at reflux for 2 hours then cooled again to room temperature. Unfortunately, this reaction was very disappointing, producing a yield of only 1 %. The second method[101] involved stirring the reagents at room temperature for 30 minutes, followed by the dropwise addition of the aldehyde and stirring for 1 hour (58 % yield). However, the best method[102] was to stir the reagents for 1 hour at 0 °C, with subsequent addition of the aldehyde **76** in tetrahydrofuran *via* a cannula and the reaction mixture stirred for 17 hours at room temperature. Purification by flash chromatography afforded the vinyl compound **45** in a yield of 91%. Subsequent hydrolysis of the vinyl ester using sodium hydroxide in dioxane released the desired acid **46** in 89%.



76 45 46

Scheme 2-23: Synthesis of ligand **46**: **i**- methyltriphenylphosphonium bromide, potassium *tert*-butoxide, tetrahydrofuran, 17 h, 0 °C-r.t., 91 %; **ii**- sodium hydroxide (1 M), 1,4-dioxane, r.t., 17 h, then hydrochloric acid (2 M), 5 min, 89 %.

A mixture of the acid **46,** di-*iso*-propylcarbodiimide and 1-hydroxybenzotriazole was added to the amino polystyrene resin for loading. After 18 hours of rotation, the resin was washed to afford the polymer-supported ligand **47** whose Kaiser test[91] proved to be negative (no free amino group). Ligand **47** was then treated 5 times with 0.1 equivalents of Grubbs first generation catalyst in degassed 1,2-dichloroethane, filtered and dried to afford the desired vinyl-supported initiator **41** (Scheme 2-24).

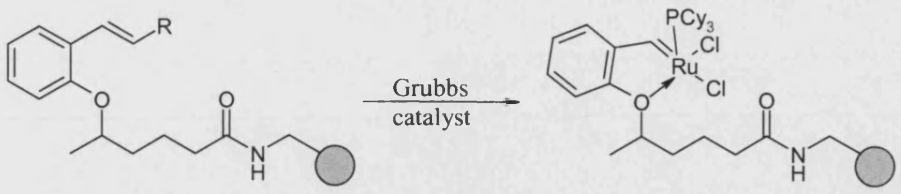


46 47 41

Scheme 2-24: Synthesis of vinyl-supported initiator **41**: **i**- di-*iso*-propylcarbodiimide, hydroxybenzotriazole, dichloromethane:dimethylformamide 1:1, r.t., 18 h; **ii**- Grubbs catalyst **3** (5 x 0.1 eq), degassed 1,2-dichloroethane, r.t., 5 x 2 h.

2.6 Testing and comparison of propenyl/vinyl-supported initiators

The efficiency of initiators **41**, made from 5-(2-(vinylphenoxy)hexanoylamino-polystyrene **47**, and **53**, made from 5-(2-(prop-1-enyl)phenoxy)hexanoylamino-polystyrene **52**, was compared by using substrates previously synthesised as decribed earlier. The results of the various reactions are shown in Table 2-3 below.



R = CH_3, **52**
R = H, **47**

R = CH_3, **53***
R = H, **41***

Scheme 2-25: Polymer-supported initiators where **41** contains remaining vinyl function and **53** contains remaining propenyl function. (*each initiator includes a proportion of free ligand)

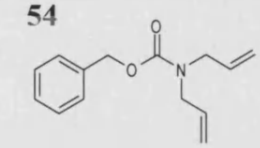
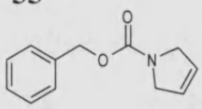
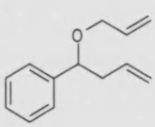
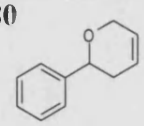
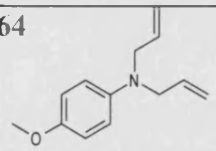
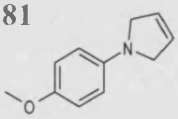
Use				1	2	3	4
Entry	**Substrates**	**Products**	**Initiator**	**conv. %[a]**	**conv. %[a]**	**conv. %[a]**	**conv. %[a]**
1	**54** 	**55** 	**53**	56	8	-	-
2			**41**	99	83	73	30
3	**58** 	**80** 	**53**	0	-	-	-
4			**41**	97	72	-	-
5	**64** 	**81** 	**53**	2	-	-	-
6			**41**	72	7	-	-

Table 2-3: Rate of conversion of ring-closing metathesis using **41** and **53**. "conv.": conversion; "-": conversion not determined; [a] Relative integration of ^{1}H NMR.

Entries 2, 4 and 6 of Table 2-3 confirm the superiority of vinyl-supported initiator, in the ring-closing metathesis of carbamate **54**, ether **58** and amine **64**. While the propenyl-supported initiator does not convert diallyl ether substrate **58** (entry 3) and poorly diallyl amine **64** (entry 5), initiator **41** gives high yields of conversion for both compounds (entries 4 and 6). However, the recyclability of vinyl-supported pre-catalyst **41** with substrate **64** did not show good results (entry 6).

The efficiency of propenyl-supported initiator **53** after the first use is nearly non-existent compared to vinyl-supported initiator **41** which still shows good recyclability. There are three likely explanations for this observation. Firstly, it may indicate that residual (non-complexed) Grubbs catalyst remaining after washing of the loaded resin is

responsible for the ring-closing metathesis explaining the poor recyclability. It may also be complexed *via* residual backbone vinyl groups in an analogous manner to Barretts' boomerang resin. Another possibility is that the polymer-supported initiator itself was not recyclable. These possibilities were tested by performing the same protocol for loading Grubbs catalyst on acetylated aminomethyl-polystyrene resin which is not capable of supporting ruthenium carbene (without ligand). The resulting resin was used for ring-closing metathesis of the diallyl carbamate substrate **54**, which did not show any significant conversion, and consequently, we concluded that the washing system of the resin is sufficient to remove all traces of Grubbs catalyst. However, as the efficiency and recyclability of the propenyl-supported initiator **53** proved to be poor, it is possible that the loading of Grubbs catalyst onto the ligand **52** is not effective or **53** is not recyclable.

Saturation of the solid-supported ligand (vinyl for **47**, alkenyl for **52**) does not occur, as sub-stoichiometric quantities of Grubbs catalyst are used, thus leaving 'vacant' ligand sites. The methylidene ruthenium **27** (Figure 2-2) is the actual catalytic species and has a relatively short half-life of approximately thirty minutes in dichloromethane.[86] For successful catalytic activity in olefin metathesis and therefore recycling, this species must be promptly intercepted by the excess of vacant ligand otherwise it will decompose. Its decomposition is observed due to change of the colour of the resin from brown to black. The reaction to recapture the methylidene ruthenium species **27** occurs more rapidly for the vinyl ligands, compared to the alkenyl ligands. In other words, recovery *via* olefin metathesis takes more time for substituted alkenes (propenyl ligand **52**), so the methylidene is more likely to decompose than with vinyl ligand **47**, ultimately leading to a difference in the level of recycling observed for each pre-catalyst.

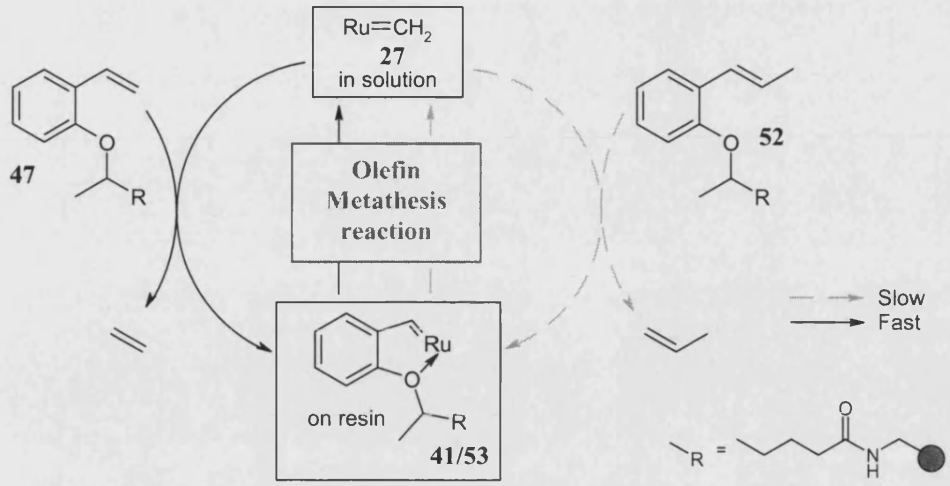


Figure 2-2: Catalytic cycle of a "boomerang" catalyst.

2.7 Summary

The synthesis of the initial vinyl-supported pre-catalyst **41** proved to be problematic due the formation of the unstable vinyl phenol, which polymerises. As the ligand reacts *via* olefin metathesis with Grubbs catalyst to form the initiator, we thought of using commercially available propenyl phenol as starting material forming a propenyl-supported ligand. By using such starting material, polymerisation was avoided, but unfortunately, the reactivity of the propenyl-supported pre-catalyst was not comparable to initiator **41**.

As the vinyl moiety is important for the reactivity of the initiator, we thought of introducing this functional group at a later stage by performing a Wittig reaction on protected salicylaldehyde. Unfortunately, this intermediate showed sensitivity to atmospheric moisture leading to deprotection, consequently the following Mitsunobu reaction did not work.

The formation of a bromo version of synthetic methyl 5-hydroxyhexanoate **42** allowed the alkylation of the salicylaldehyde. The aldehyde moiety was then subjected to a Wittig reaction forming the vinyl intermediate which was hydrolysed to produce the acid, precursor of the polymer-supported ligand. The resulting initiator was finally tested and compared to the propenyl-supported initiator in ring-closing metathesis reactions with different acyclic diene substrates.

Comparing the activities of the vinyl- and propenyl-supported initiators (**41** and **53** respectively), shows the high efficiency of **41**. The new synthetic pathway affords the

powerful polymer-supported initiator without altering its efficiency when used for olefin metathesis reactions. The difference in recycling of vinyl- versus propenyl-derived resins was initially surprising, but can be explained by the difference in the ability of the vinyl and propenyl ligands to recapture the methylidene ruthenium species **27**. For successful catalytic activity and therefore recycling, this reactive species must be promptly intercepted by the excess of vacant ligand otherwise decomposition will occur.

3.0 Exploration of initiator substituents

Second generation Grubbs ruthenium catalyst **7** (Scheme 3-2) is a derivative of the first generation Grubbs benzylidene ruthenium complex **3** (Figure 1-2). Exchanging phosphine for a carbene ligand is known to afford a more stable and active complex, which can react with tri- and tetra-substituted alkenes.[32] As mentioned in the introduction (1.1.3 mechanism), the electron-donating ability of the *N*-heterocyclic carbene stabilizes the propagating complex and helps the formation of the metallacyclobutane intermediate before the phosphine ligands can re-associate to the propagating species.

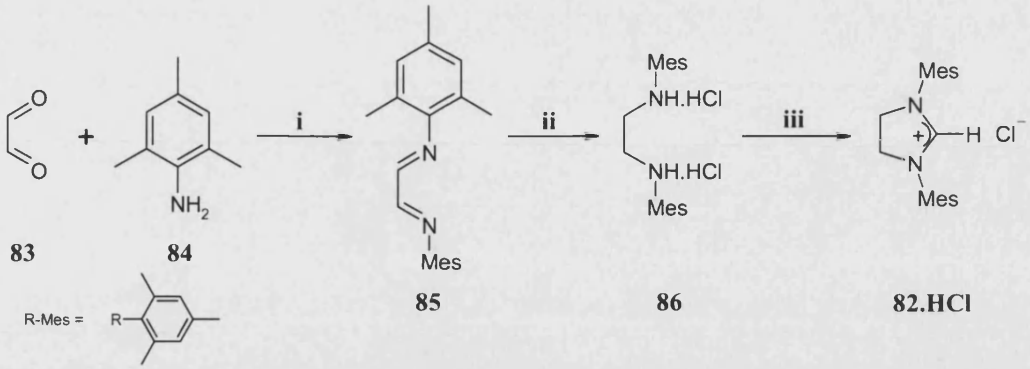
With our aim being to improve the efficiency of our initiators, it was decided to attach an *N*-heterocyclic carbene in place of one of the phosphines in order to optimise the catalytic properties of the immobilized pre-catalyst.

The efficiency of first and second generation polystyrene ligands was compared and a new initiator was synthesised carrying a hydrophilic polymer (PEGA) instead of polystyrene, with the aim of examining the olefin metathesis activity of the initiators in polar solvents. The final modification was the addition of a functional group to the phenyl moiety of the supporting ligand in order to increase the electronic effect, improving the dissociation of the *O*-^{i}Pr group during the initiation and therefore increasing the speed of the reaction.

3.1 Second generation aminopolystyrene- and PEGA-supported initiators

3.1.1 Synthesis of second generation Grubbs catalyst 7

1,3-*Bis*(2,4,6-trimethyphenyl)-4,5-dihydroimidazolium salt ligand **82** was synthesised following Arduengo's method (Scheme 3-1).[90] Addition of trimethylaniline **84** in propanol to a solution of glyoxal **83** in water resulted in a yellow mixture which crystallised to afford diimine **85** which was then reduced to give hydrochloride **86**. Ligand **82.HCl** was obtained by heating **86** at reflux with triethyl orthoformate and formic acid and distilling the resulting ethanol, affording the ligand in a yield of 89 %.[90]



Scheme 3-1: Synthesis of hydrochloride ligand **82.HCl**: **i**- *n*-propanol, r.t., 16 h, 76 %; **ii**- a) sodium borohydride, anhydrous tetrahydrofuran, r.t., 16 h, b) H_2O, HCl, 5 min, 85 %; **iii**- triethyl orthoformate, formic acid (90 %), distillation at 140 °C, 89 %.

Initially, ligand **82.HCl** was added to potassium *tert*-butoxide, but this does not dissolve in hexane leading to longer reaction times and therefore to low yields.[103] It has been shown that a four-coordinate complex **87** (Figure 3-1) which proves to be inactive in ring-closing metathesis is obtained if extensive heating is attempted to dissolve the base in hexane.[104]

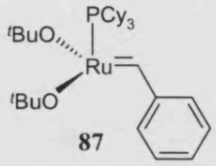
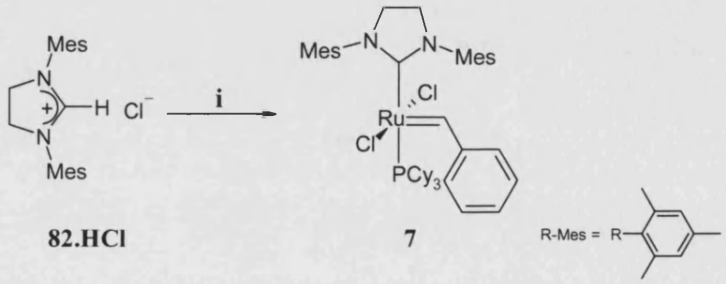


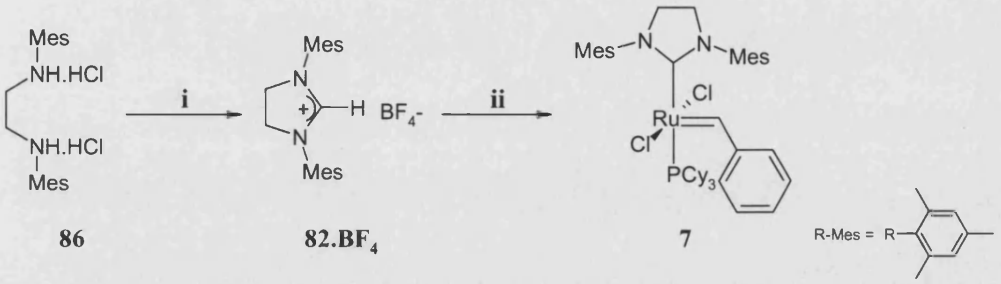
Figure 3-1: Four-coordinate ruthenium complex **87**.

Nolan developed a convenient one-pot synthesis of second generation catalyst using potassium *tert*-pentylate which is more soluble and retains its basic properties leading to rapid conversion of the salt ligand to the free carbene.[104] The reaction was performed in degassed hexane and stirred for 2 h at room temperature. Following the addition of Grubbs catalyst, the reaction mixture was stirred for 1 h at room temperature and a further 3 h at 50 °C. The resulting solution was purified by column chromatography to furnish the second generation catalyst **7** in a yield of 3 % (Scheme 3-2).



Scheme 3-2: Synthesis of second generation Grubbs catalyst **7**: **i**- a) potassium *tert*-pentylate in toluene (1.7 M), degassed hexane, r.t., 2 h, b) Grubbs catalyst, degassed hexane, r.t., 1 h, c) 50 °C, 3 h, 3 %.

An alternative route to the second generation Grubbs catalyst **7** was devised in order to improve the yield of the final step by using the tetrafluoroborate salt instead of chloride salt **82**. Intermediate **86** was heated at reflux in the presence of ammonium tetrafluoroborate and triethyl orthoformate, affording **82.BF$_4$** (in 66 % yield) which was then added to potassium *tert*-pentylate in degassed hexane and stirred for 1.5 h at room temperature. Grubbs catalyst was then added to the reaction mixture which was then stirred for 2 hours at 60 °C affording second generation Grubbs catalyst **7** in a yield of 86 % (Scheme 3-3).[104]

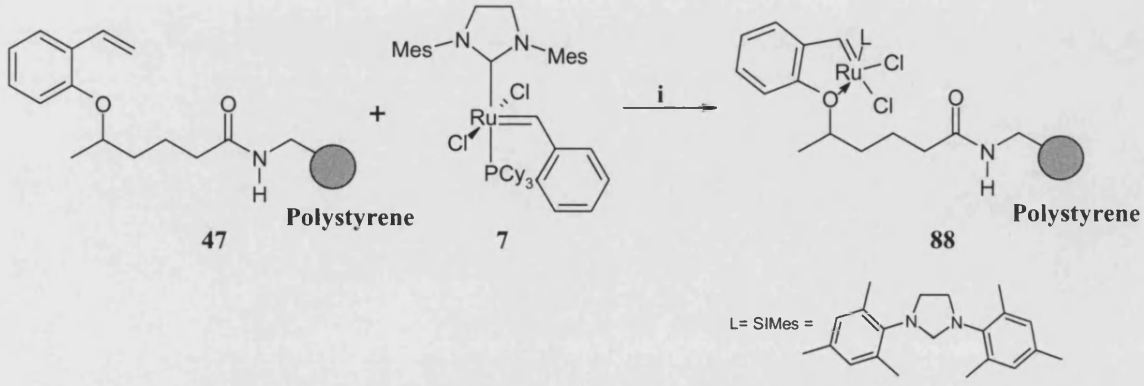


86 **82.BF$_4$** **7**

Scheme 3-3: Synthesis of second generation Grubbs catalyst **7**: **i**- ammonium tetrafluoroborate, triethyl orthoformate, reflux, 3 h, 66 %. **ii**- a) potassium *tert*-pentylate in toluene (1.7 M), degassed hexane, r.t., 1.5 h, b) Grubbs catalyst, degassed hexane, 60 °C, 2 h, 86 %.

3.1.2 Synthesis of second generation polystyrene-supported initiators.

We wanted to explore the polymer-supported version of our second generation initiator. Polystyrene-supported initiator **88** was synthesised following the same method as for the first generation pre-catalyst. Treatment of the polystyrene ligand **47** five times with 0.1 equivalent of second generation Grubbs catalyst **7** in degassed 1,2-dichloroethane at 40 °C, afforded resin **88** after filtering, washing and drying (Scheme 3-4).



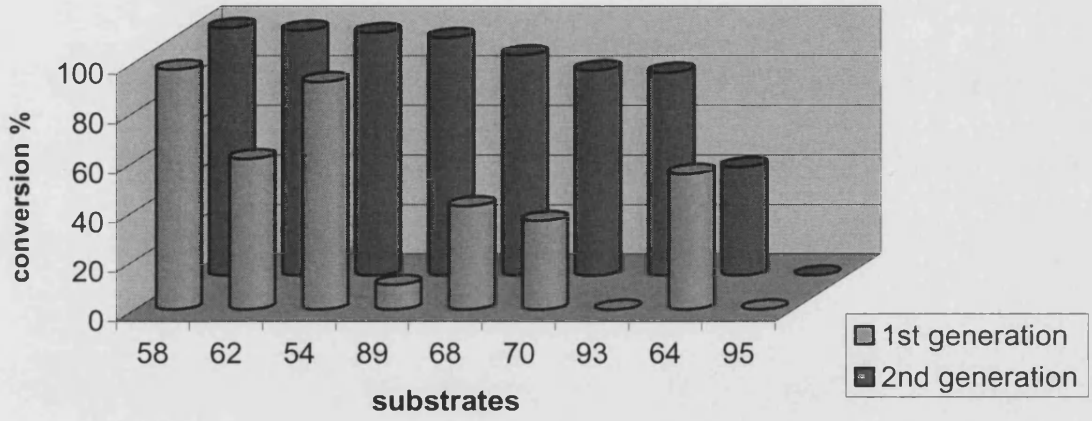
47 **7** **88**

Scheme 3-4: Synthesis of second generation polystyrene-supported initiator **88**: **i**- 1,2-dichloroethane, 40 °C, 5 x 4 h.

3.1.3 Comparison of first and second generation polymer-supported initiators

The efficiency of our first and second generation polystyrene-supported initiators **41** and **88**, for ring-closing metathesis with previously synthesised and commercially available acyclic diene substrates, was compared.

^{1}H NMR initially defined the level of conversion using relative integration, isolated yields were calculated after purification by flash chromatography where possible, and the results are given in Table 3-1 and Graph 3-1.



Graph 3-1: Comparison of the rate of conversion in ring-closing metathesis on a series of different substrates using first and second generation initiators.

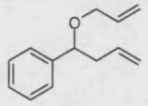
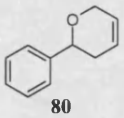
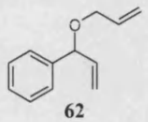
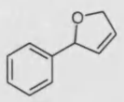
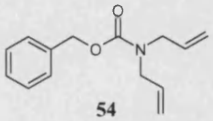
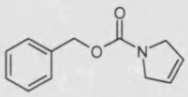
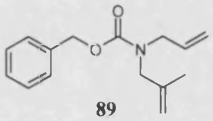
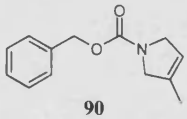
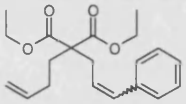
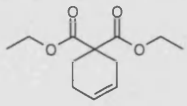
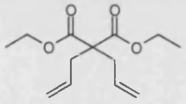
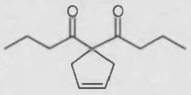
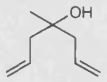
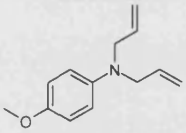
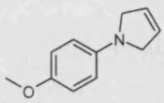
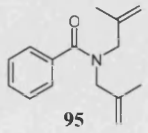
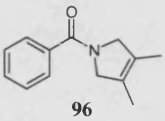
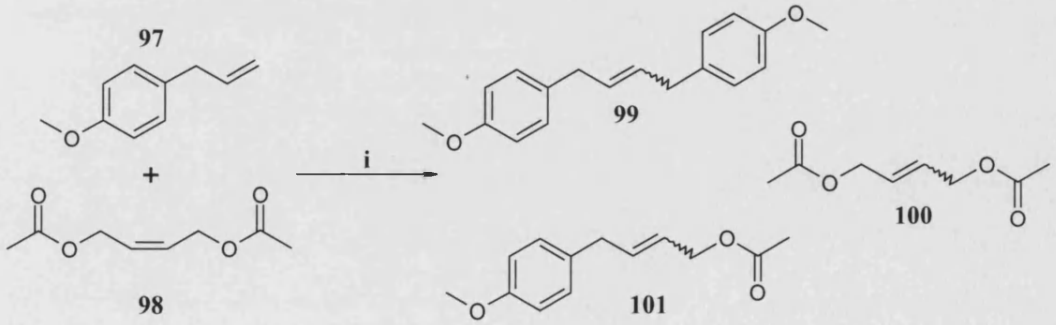
Entry	Substrates	Product	Initiator used	Conversion %[a]	Isolated Yield %
1	 58	 80	41	97	95
2			88	100	98
3	 62	 61	41	61	-[c]
4			88	99	-[c]
5	 54	 55	41	92	90
6			88	98	95
7	 89	 90	41	10	13
8			88	96	97
9	 68	 91	41	42	-[b]
10			88	89	-[b]
11	 70	 92	41	36	-[b]
12			88	83	-[b]
13	 93	 94	41	0	-[c]
14			88	82	-[c]
15	 64	 81	41	55	-[b]
16			88	44	-[b]
17	 95	 96	41	0	0
18			88	0	0

Table 3-1: Conversion and isolated yield of ring-closing metathesis and olefin cross metathesis using **41** and **88**. [a] Relative integration of ^{1}H NMR. [b] Not isolated: R_fs too similar. [c] Not isolated: Volatile product, reaction performed in deuterated chloroform.

The efficiency of the two pre-catalysts is comparable for the ring-closing of ethereal substrate **58** and carbamate substrate **54** (entries 1,2 and 5,6). As might be expected, however, second generation polystyrene-supported initiator **88** was superior for converting acyclic dienes compared to first generation **41** (Graph 3-1). Initiator **88** converts ethereal compound **62** to volatile compound **61** in 99 % (entry 4), while **41** only provides a 66 % yield (Entry 3). A similar finding was observed for the formation of volatile product **94** which does not occur when the first generation initiator is used in the ring-closing reaction (entries 13 and 14). Second generation catalysts are highly reactive allowing the olefin metathesis of substituted alkenes,[44] for example, with methyl substituted substrate **89** (entries 7 and 8), first generation initiator **41** showed a poor conversion to the *N*-heterocyclic product **90** where as second generation initiator **88** afforded the product in 96 % yield. Diene malonate **68** is substituted with a phenyl group which, during ring-closing metathesis, recovers the more stable ruthenium benzylidene, leading to a good yield of 89 % with second generation initiator **88** (entry 10). However, methyl di-substituted dienes, such as dimethyl-substituted carbamate **95** do not undergo ring-closing metathesis with either initiator (entries 17 and 18). These results might be due to the fact that the olefin metathesis of substituted alkenes is slower than for the non-substituted, therefore, the active species decomposes before turn over of the substrate, thus limiting the rate of conversion (Figure 2-2).

Commercially available compounds **97** and **98** (Scheme 3-5) were used to test the efficiency of the initiators for cross metathesis. This reaction led to a total of six different compounds composed of the *E* and *Z* isomers of the homocoupled and cross coupled compounds (Table 3-2).



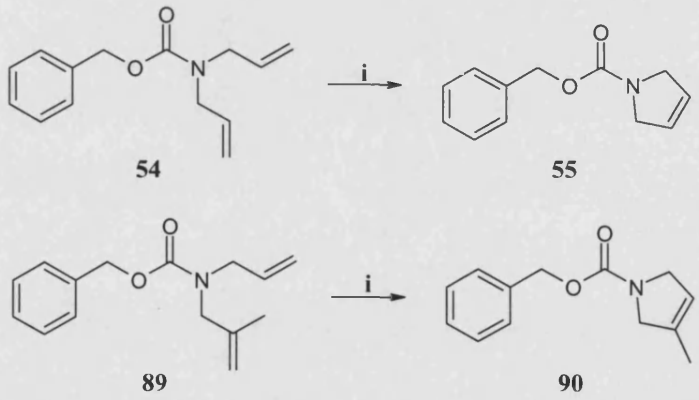
Scheme 3-5: Olefin cross-metathesis using first and second generation polystyrene initiators.

Entry	Initiator	Product	Isolated Yield %
1		**99**	33[a]
2	**41**	**100**	45[a]
3		**101**	30[a]
4		**99**	1 (*Z*:*E* 18:82)
5	**88**	**100**	27 (*Z*:*E* 12:88)
6		**101**	45 (*Z*:*E* 9:91)

Table 3-2: Isolated yield of olefin cross metathesis using **41** and **88**; yields based on the molarity of the smallest amount of substrate; [a] yields obtained previously by our group.

Entries 1, 2 and 3 shows the results obtained previously by our group using first generation polymer-supported initiator **41**. The conversion of the two allylic substrates **97** and **98** produces a majority of dimeric product **100** compared to second generation pre-catalyst **88** which produced the mixed dimer **101** (entry 6) in the highest yield with a preference for the *trans*-configuration being shown (entries 4,5 and 6) .

One of the aims of the project was to synthesise a highly efficient, recyclable initiator. Therefore, both initiators **41** and **88** were tested 4 successive times for their ability to cyclise acyclic diene substrates **54** and **89** (Scheme 3-6).

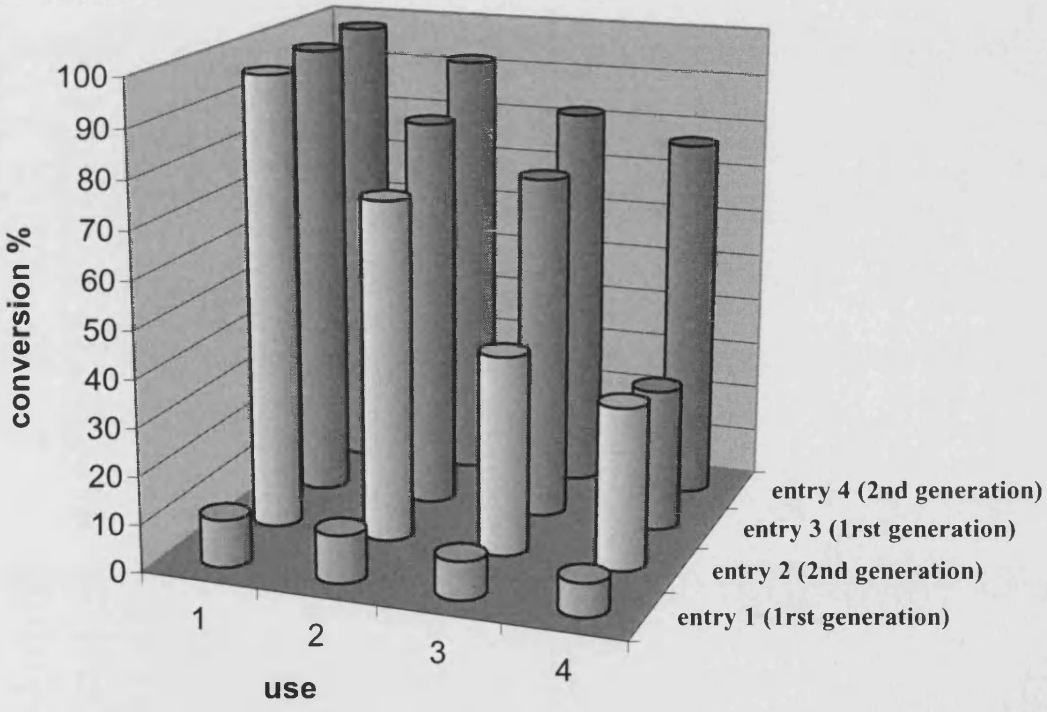


Scheme 3-6: Substrates used to test the recyclability of first and second generation initiators **41** and **88**: **i**- **41** or **88**, dichloromethane, 90 min, r.t..

After each use, the resin was washed, dried and re-used in ring-closing metathesis. The filtrate was concentrated and analysed using ^{1}H NMR which initially defined the extent of conversion using relative integration. Isolated yields were calculated after purification by column chromatography and the results are given by Table 3-3 and Graph 3-2.

uses			1		2		3		4	
Entry	Substrates	Initiator used	% conv.[a]	i.y.	% conv.[a]	i.y.	% conv.[a]	i.y.	% conv.[a]	i.y.
1	89	41	10	13	10	11	8	7	7	-
2		88	96	97	72	78	42	40	34	30
3	54	41	97	97	83	81	73	70	30	29
4		88	98	95	92	94	82	82	77	76

Table 3-3: Conversion and isolated yield of ring-closing metathesis after 4 uses of the initiator. [a] Relative integration of ^{1}H NMR. i.y.: isolated yield.



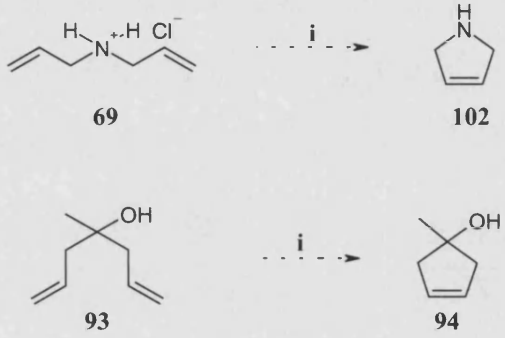
Graph 3-2: Conversion of ring-closing metathesis after 4 uses of the initiator.

The activity of second generation initiator **88** with non-substituted alkenes has already been demonstrated to be higher than first generation, but its good recyclability was demonstrated here. It was also known that olefin metathesis of substituted alkenes is slower than for non-substituted leading to decomposition of the active species therefore

decreasing reactivity after several uses. This explains the high conversion after the first use of **88** with substituted alkene **89** and the regular decrease in activity afterwards. To conclude, second generation initiator **88** shows a better recyclability than first generation initiator **41** even with substituted alkenes.

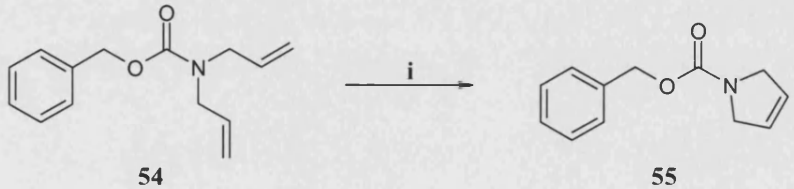
We are interested in creating an initiator that we could potentially use to assemble inhibitors in the presence of a biological target and therefore, we tested the efficiency of our initiator in water with a series of water-soluble substrates.

Ring-closing of water-soluble diallylammonium chloride **69** and di-prop-2-enyl ethanol **93** in water using pre-swollen aminopolystyrene-supported initiator **88** was performed (Scheme 3-7). Washing of the resulting resin with water did not show any converted product by ^{1}H NMR nor starting material.



Scheme 3-7: Ring-closing metathesis of diallylammonium chloride **69** and di-prop-2-enyl ethanol **93** using second-generation initiator **88** in water: **i- 88** pre-swollen in dichloromethane, D_2O.

Pre-swollen initiator **88** in toluene was tested in the ring-closing metathesis of diallyl carbamate **54** in water. The ^{1}H NMR analysis of the filtrate showed no conversion to the cyclised product. It is possible that the substrate remains in the toluene used to pre-swell the polystyrene resin and after washing the resin with dichloromethane the ^{1}H NMR showed a conversion of 56 %. This may be because the organic substrate stayed captured in the resin and was only released when washed by non-protic solvents (Scheme 3-8).

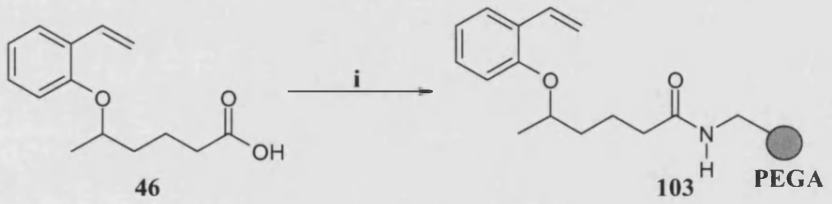


Scheme 3-8: Ring-closing metathesis of compound **54** using second-generation initiator: **i- 88**, water, 56 %.

This series of tests using water-soluble acyclic dienes as substrates, show that the second-generation polystyrene-supported initiator **88** is not efficient in water, only in non-protic solvents because it is not able to swell in polar solvents. However, it might be possible to improve its efficiency in polar solvent by altering the solid support used from polystyrene to a hydrophilic resin able to swell in water, such as amino PEGA.

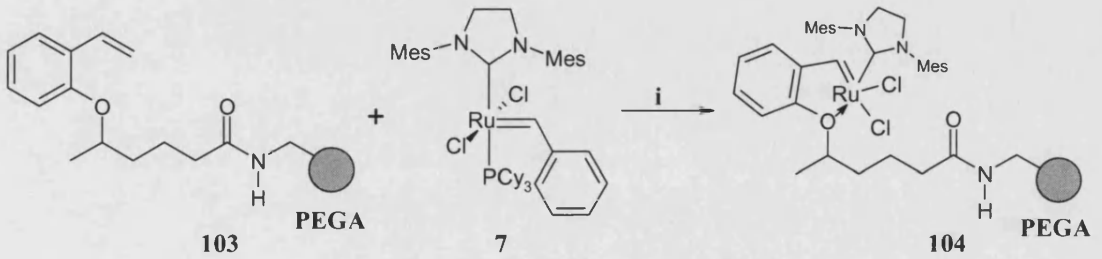
3.1.4 Synthesis of second generation amino-PEGA-supported initiator

In order to develop a second generation vinyl-supported initiator efficient in polar solvents, second generation amino-PEGA-supported initiator was synthesised. To the previously synthesised acid **46** were added di-*iso*-propylcarbodiimide and 1-hydroxybenzotriazole and this mixture was added to the amino-PEGA resin for loading. After 24 hours, the resin was washed and acylation of the resin performed using triethylamine, DMAP and acetic anhydride. The reaction mixture was then agitated for 16 hours, washed and rinsed to afford the polymer-supported ligand **103** (Scheme 3-9).



Scheme 3-9: Synthesis of PEGA-supported vinyl ligand **103**: **i**- a) di-*iso*-propylcarbodiimide, hydroxybenzotriazole, dichloromethane:dimethylformamide 1:1, r.t., 15 h; b) triethylamine, DMAP, acetic anhydride, dichloromethane, r.t., 20 h.

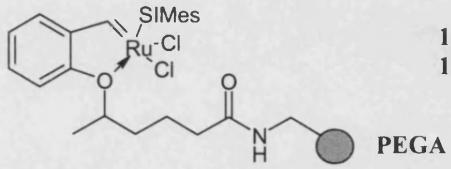
A small portion of the resin was subjected to the Kaiser test[91], which was negative (no free amino group). PEGA-supported ligand **103** was then treated 5 times at 40 °C with small portions of previously synthesised second generation Grubbs catalyst **7** in degassed 1,2-dichloroethane, filtered, washed with dichloromethane and dried to afford the resin **104** (Scheme 3-10).



Scheme 3-10: Synthesis of second generation PEGA-supported initiator **104**: **i**- **7** (5 x 0.1 eq), degassed 1,2-dichloroethane, 40 °C, 5 x 4 h.

3.1.5 Amino-PEGA-supported initiator used in olefin metathesis in polar solvents

A series of substrates, soluble in polar solvents, were tested with second generation amino-PEGA-supported initiator **104** in ring-closing metathesis and acyclic cross-metathesis under different conditions. Second generation vinyl-supported catalyst **104** was compared to second generation propenyl-supported initiator **105** (Figure 3-2) which was previously synthesised by our group.[89]



104 = from vinyl ligand
105 = from propenyl ligand

Figure 3-2: Initiators used in polar solvent in olefin metathesis reactions.

^{1}H NMR initially defined the extent of conversion using relative integration, isolated yields were calculated after purification by column chromatography and the results are given in Table 3-4.

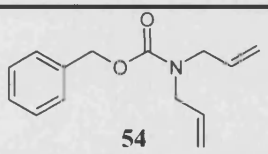
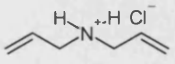
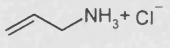
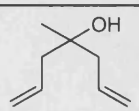
Entry	Compound	Solvent	T °C	Catalyst	Conversion %[a]	Isolated yield %[b]
1		$CDCl_3$	r.t.	**104**	>99	95
2		MeOH	r.t.	**104**	68	69
3	**54**	MeOH	r.t.	**105**	38	-
4		MeOH	r.t.	**104**	42	40
5		D_2O	r.t.	**104**	51	51
6	**106**	D_2O	45	**104**	85	87
7		MeOH	r.t.	**104**	50	47
8		D_2O	r.t.	**104**	3	-[c]
9	**69**	D_2O	45	**104**	7	-[c]
10		MeOH	r.t.	**104**	0	-
11		D_2O	r.t.	**104**	0	-
12	**107**	D_2O	45	**104**	0	-
13		CD_3OD	r.t.	**104**	28	-[d]
14		D_2O	r.t.	**104**	57	-[d]
15	**93**	D_2O	45	**104**	47	-[d]

Table 3-4: Use of second generation PEGA-supported initiators in polar solvents: 90 minutes on a blood rotator for reactions at room temperature, and in a water bath for those at 45 °C. [a] Relative integration of ^{1}H NMR; [b] yield after purification using flash chromatography; [c] ~ 0 %; [d] volatile.

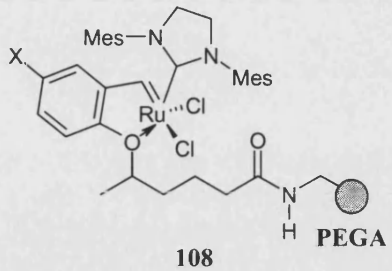
Firstly, vinyl-derived second generation PEGA-supported initiator **104** was tested with carbamate substrate **54** in deuterated chloroform (entry 1) and showed an efficiency comparable to the equivalent polystyrene-supported initiator **88**. Then, vinyl- and propenyl-PEGA-supported initiators **104** and **105** were tested with the same substrate for ring-closing metathesis in methanol (entries 2 and 3) and as expected, vinyl-supported initiator **104** showed better conversion and was therefore used in all following olefin metathesis reactions. Ring-closing metathesis of diallylammonium chloride **69** did not show any conversion in D_2O compared to diallylethanol **93** which was most efficiently converted in the same solvent. Acyclic cross metathesis of allyl alcohol **106** in D_2O at 45 °C afforded a good conversion of 85 % (entry 6) which is the best result observed with this substrate, while this reaction did not occur with allyl ammonium chloride. During these tests, Blechert's group published similar findings[79], with his version of second generation Hoveyda type PEGA-supported initiator **30** (Figure 1-13) producing similar results for cross-metathesis compared to our second generation PEGA-supported initiator **104**. However, ring-closing metathesis of diallylammonium chloride **69**, was slightly improved when compared to initiator **104** in both water and methanol.

3.2 Nitro and methoxy substituted analogues

3.2.1 Synthesis of nitro and methoxy substituted analogues

Previously synthesised initiators (**88** and **104**) show good results in ring-closing metathesis and cross-metathesis, however, with some substrates the reaction remains slower than using second generation catalyst **7**. We thought that adding a functional group to the phenyl moiety of the supported ligand would alter its electronic properties and change its behaviour. This could improve its dissociation and therefore increase the speed of the reaction and the efficiency of the initiator. The second generation analogues follow the design described in Figure 3-3 (**108**), with the desired functional group (X) *meta* relative tothe vinyl moiety on the phenyl ring and the presence of the imidazolylidene ligand which is known to increase the efficiency of the initiator. Amino PEGA resin is used as solid support as it shows the same efficiency as polystyrene in organic solvents while providing activity in protic solvents as shown previously (3.1.5). The analogues were compared to the initial second generation initiator for olefin cross-metathesis, and a kinetic study showed whether or not addition of the functional group

increases the speed of reaction. Examination of the recycling of these analogues was also of interest.

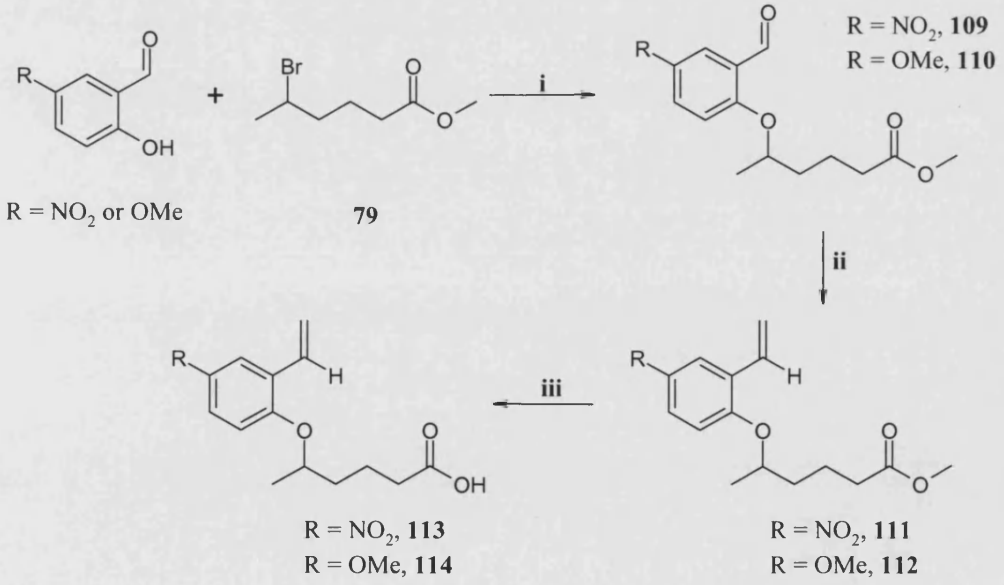


108

Figure 3-3: Model of the target analogues where X is a functional group adding an electronic effect to the ligand.

The synthesis of the nitro and methoxy analogues was performed following the same procedure, therefore only the synthesis of the nitro analogue will be discussed with the yields of the methoxy analogue shown in parenthesis.

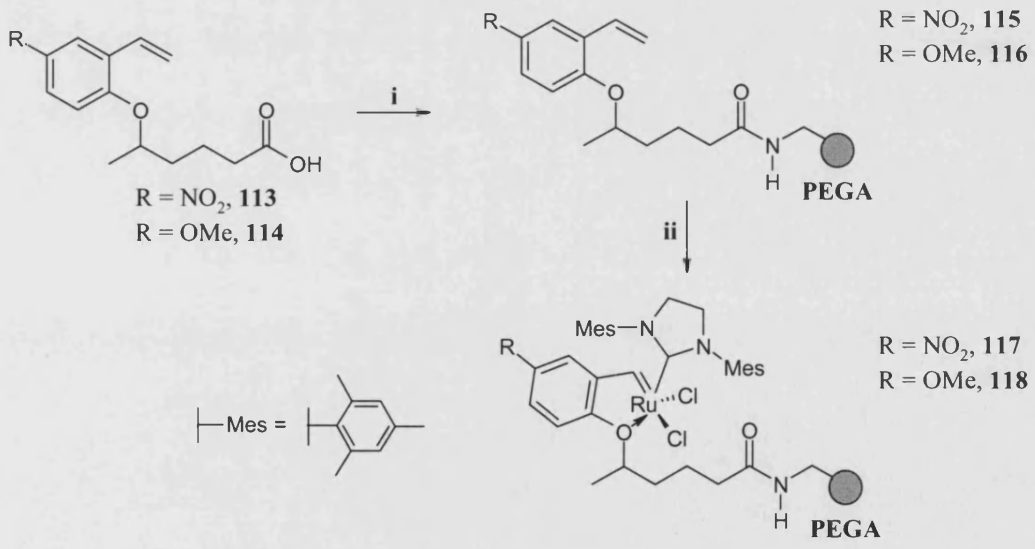
Following the previously reported procedure to synthesise ethereal compound **76**,[105] potassium carbonate was added to commercially available 2-hydroxy-5-nitro-benzaldehyde in dimethylformamide and stirred for 1.5 hours. The previously synthesised bromo compound **79** was then added *via* a cannula to afford methyl 5-(2-formyl-4-nitrophenoxy)hexanoate **109** in 53 % yield (70 % for **110**) (Scheme 3-11).



Scheme 3-11: Synthesis of vinyl acid **113** (and **114**): **i**- potassium carbonate, anhydrous dimethylformamide, 17 h, 60 °C, 53 % (70 %); **ii**- methyltriphenylphosphonium bromide, potassium *tert*-butoxide, tetrahydrofuran, 17 h, 0 °C-r.t., 55 % (85 %); **iii**- a) sodium hydroxide (1 M), 1,4-dioxane, r.t., 17 h; b) hydrochloric acid (1 M), 5 min, 68 % (97 %).

The next stage in the synthesis of the nitro-analogue was the Wittig reaction[102] that converts the aldehyde functionality to a vinyl group. Methyltriphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran were stirred for 1 hour at 0 °C, followed by addition of the aldehyde **109** (or **110**) *via* a cannula to the reaction mixture which was then stirred for 17 hours at room temperature. Purification by flash chromatography furnished the vinyl compound **111** in 55 % yield (85 % for **112**), which was hydrolysed using sodium hydroxide, releasing the desired acid **113** in 68 % yield (97 % for **114**).

The acid **113** (or **114**) was then attached to PEGA resin, chosen because of its hydrophilic property giving the supported initiators good efficiency in both polar and non-polar solvents. Di-*iso*-propylcarbodiimide and 1-hydroxybenzotriazole were added to the acid **113** (**114**) and this mixture was added to a suspension of amino-PEGA resin in dimethylformamide for loading. After 24 hours at room temperature, the resin was washed and acylation of the resin was performed using triethylamine, DMAP and acetic anhydride. The reaction mixture was then agitated using a blood rotator for a further 16 hours at room temperature and rinsed to afford polymer-supported ligand **115** (**116**) (Scheme 3-12).



Scheme 3-12: Synthesis of second generation initiator nitro and methoxy-PEGA analogues **117** and **118**; **i**- a) di-*iso*-propylcarbodiimide, hydroxybenzotriazole, dichloromethane:dimethylformamide 1:1, r.t., 24 h, b) triethylamine, DMAP, acetic anhydride, dichloromethane, r.t., 20 h; **ii**- 5 x 0.1 eq. of **7**, degassed 1,2-dichloroethane, 45 °C, 4 h.

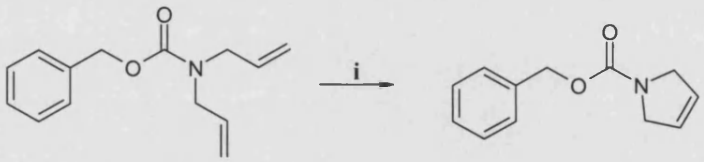
A small portion of the resin was subjected to Kaiser test[91], which was negative (no free amino group). Ligand **115** (**116**) was then treated 5 times at 45 °C with small portions of

previously synthesised second generation Grubbs catalyst **7** in degassed 1,2-dichloroethane, filtered, washed with dichloromethane and dried to afford the initiator **117** (**118**) as brown beads (green beads).

The newly synthesised nitro and methoxy second generation PEGA-supported analogues were tested in ring-closing metathesis to determine if an increase in efficiency was observed when compared to second generation PEGA-supported initiator **104**. Firstly, a kinetic study showed us how the differing electronic properties of the new ligand affected the speed of the reaction and subsequently, their recyclability was tested.

3.2.2 Comparison of second generation PEGA-supported initiator 104, 117 and 118 in ring-closing metathesis

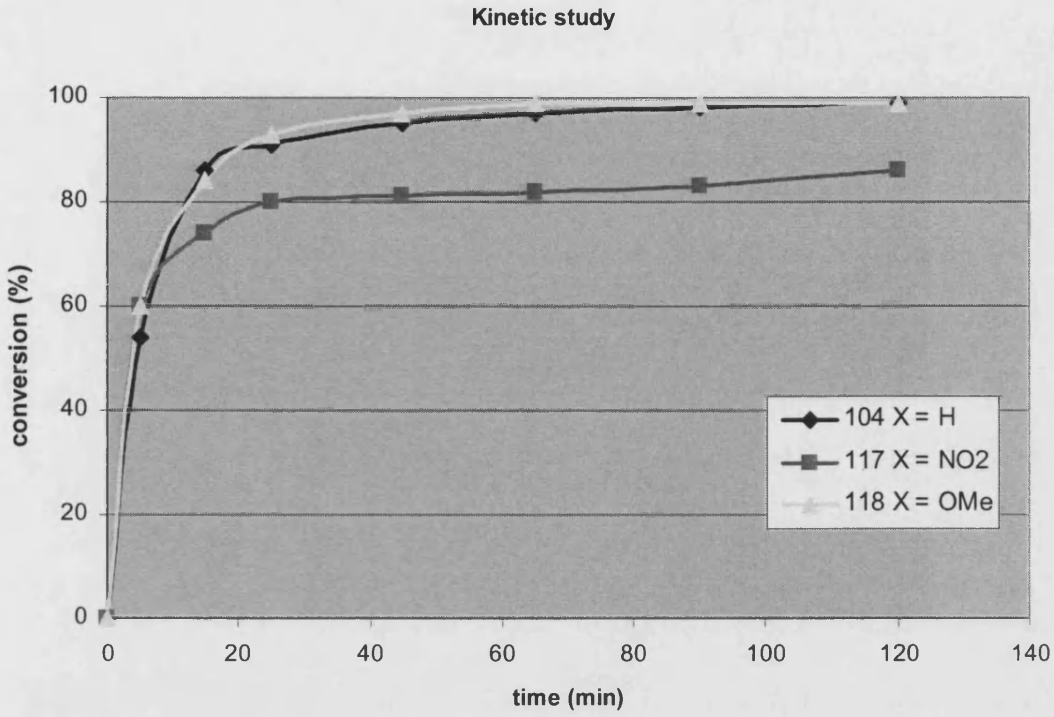
Second generation PEGA-supported initiators **104**, **117** were compared for ring-closing metathesis with previously synthesised acyclic diene carbamate **54** (Scheme 3-13).



54 **55**

Scheme 3-13: Ring-closing metathesis of carbamate **54** testing the recyclability of second generation PEGA-supported initiators **117** and **118**: **i**- **117** or **118**, $CDCl_3$, 90 min, r.t..

Seven parallel reactions were set up in plastic solid-phase synthesis tubes, each containing diallyl carbamate substrate **54** and resin (**117**, **118** or **104**) in deuterated chloroform and agitated at room temperature for 5, 15, 25, 45, 65, 90 or 120 minutes. Filtration and washing with deuterated chloroform directly into an NMR tube allowed the extent of conversion using relative integration to be measured Graph 3-3.



Graph 3-3: Kinetic study of nitro and methoxy analogues with initial **104**.

It is noticeable that during the first five minutes, the two second generation PEGA-supported analogues show slightly better conversion levels than **104**. However, subsequent time points show the nitro substituted initiator to be less efficient than the other two. After 20 minutes, the reaction is almost complete for both the methoxy analogue **118** and **104** (>95 %). It is important to note that the loading of Grubbs catalyst onto each resin may differ affecting their catalytic activity and for this reason elemental ICP-MS analysis was performed to determine the quantity of ruthenium present in each initiator (Table 3-5).

entry	initiator	Ru ($mmol_{Ru}/g_{initiator}$)
1	**104**	0.109
2	**117**	0.078
3	**118**	0.106

Table 3-5: Analytical studies of concentration of ruthenium in the initiators.

These results may explain why the nitro-analogue shows a lower reactivity as the amount of ruthenium and therefore the amount of active species is lower than in the two other initiators. This could be due to less effective loading of the second generation Grubbs catalyst onto the nitro ligand, or simply rapid decomposition of the initiator due

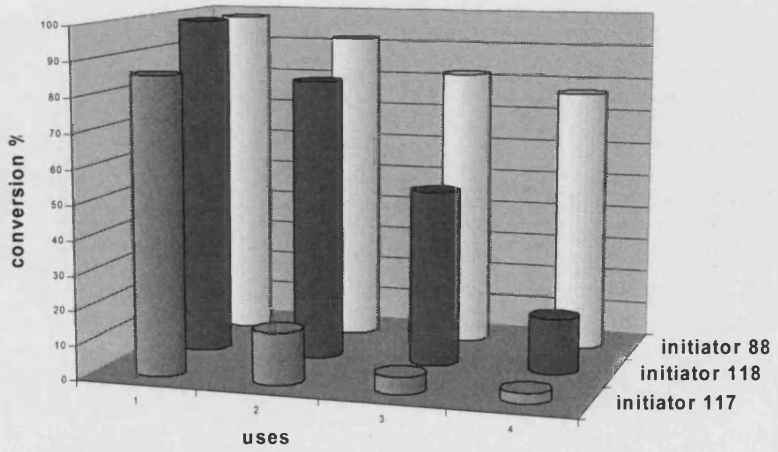
to instability. However, the literature shows an increase in the efficiency of the Hoveyda initiator **10** when a nitro group is added to the phenyl moiety of the ligand[106] which does not correlate with our results. The only difference between our nitro analogue and Grela's is the solid support, but it seems surprising that this difference affects the catalytic activity of the pre-catalyst.

The addition of a functional group to the ligand has an electronic effect on the initiator, which is supposed to increase the speed of the reaction. This would mean a faster release of the active species **27** and consequently a higher efficiency in olefin metathesis. Both initiators **117** and **118** were tested after 4 successive uses with diallyl carbamate **54** (Scheme 3-13) and the results were compared to those of second generation polystyrene-supported initiator **88**.

A mixture of carbamate **54** and resin (**117** or **118**) in deuterated chloroform was sealed in a plastic solid phase synthesis tube and was agitated by 360° rotation at room temperature for 90 minutes. Following each use, the resin was washed with dichloromethane, dried and reused in ring-closing metathesis. ^{1}H NMR initially defined the extent of conversion using relative integration and the results are given in Table 3-6 and graph 3-4.

use		1	2	3	4
entry	**initiator**	**conv. %**	**conv. %**	**conv. %**	**conv. %**
1	**117**	86	15	5	3
2	**118**	99	82	51	16

Table 3-6: Recyclability of nitro and methoxy analogues **117** and **118** as determined by integration of ^{1}H NMR.



Graph 3-4: Comparison between second generation polystyrene-supported initiator and PEGA analogues in their recyclability.

The results show that the recyclability of the nitro and the methoxy second generation PEGA-supported initiators is inferior to second generation polystyrene-supported initiator **88**. Firstly, the nitro analogue, which was already showing lower catalytic activity, proved to be practically inactive after its first use, while the methoxy analogue showed a constant loss of activity after each use. The addition of a functional group might have added an electronic effect allowing a more rapid release of the ligand during the initiation of the reaction, but, unfortunately it does not seem to allow reattachment of the active species as quickly and consequently decomposition occurs explaining the poor recyclability.

3.3 Summary

The development of the second generation analogue of our first generation vinyl polystyrene-supported initiator **41** proved to have a higher efficiency with most of the substrates used, as well as a higher recyclability. This was as expected because the exchange of a phosphine ligand for a carbene is known to afford a more stable and active complex due to their differing electronic properties.[32]

As second generation polystyrene-supported initiator **88** showed no activity when used in water, it was decided to replace the polystyrene support with a hydrophilic resin which afforded second generation PEGA-supported initiator **104**. This initiator showed catalytic activity for olefin metathesis performed in polar solvents, especially for the cross metathesis of allyl alcohol in water at 45 °C (85 %).

The development of a second generation PEGA-supported initiator has already shown good results, however, we attempted to improve their efficiency by substituting the phenyl moiety of the ligand with nitro and methoxy functionalities. This technique increases the electronic effect of the ligand, accelerating the dissociation of the *O*-^{i}Pr moiety during the initiation of the olefin metathesis reaction. The kinetic study of the methoxy-analogue showed a comparable efficiency with second generation PEGA-supported initiator **104**. However, its recyclability is not comparable and its efficiency decreases regularly after each use. The nitro-analogue showed a lower activity than the two other initiators which may be due to a difference in the effectiveness of the loading of Grubbs second generation catalyst during the synthesis of the initiator. A further effect of this modification was that its recyclability was very poor.

As one of our aims is to assemble inhibitors in the presence of a biological target, the development of a catalyst efficient in polar solvents such as water would be useful. We therefore planned to modify the imidazolylidene ligand which is specific to the efficient second generation catalyst in order to alter the solubility of the new pre-catalyst in a variety of solvents.

4.0 Aiming for biological compatibility

Olefin metathesis is useful in the synthesis of potential drug compounds as it can be used as a convenient method to link molecules together. Developing olefin metathesis to operate under biologically compatible conditions may permit the synthesis of potential inhibitors in the presence of a biological target, such as a protein (Figure 4-1). The presence of alkenes in biomolecules is rare and therefore secondary reactions with proteins will be limited.

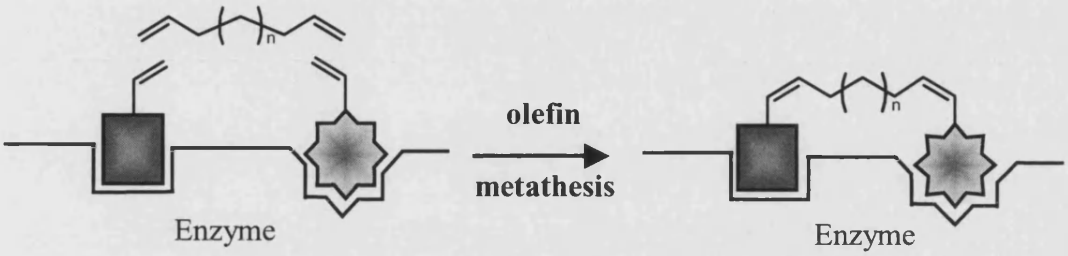
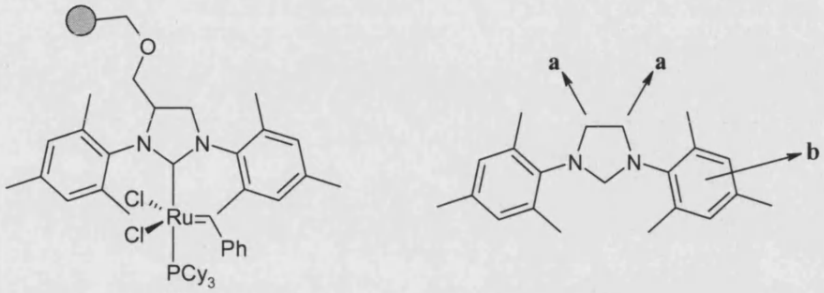


Figure 4-1: Molecules targeting different portions of the binding site of the bio target (protein, enzymes) linked together using olefin metathesis.

It is known that ruthenium carbene olefin metathesis catalysts decompose in the presence of water and primary alcohols to form a hydride complex **37** (or **39**, Figure 1-17).[87] As our aim was to synthesise a small library of possible biologically active molecules, it would be interesting to perform synthesis in such polar solvents. With this in mind, we decided to develop the synthesis of new ligands that would improve the activity of our initiators when used in polar solvents. These ligands follow the design of previously synthesised *N*-heterocyclic carbene ligand **82** (Scheme 3-3), which was used to form the more stable and efficient second generation catalyst **7**. Addition of a functional group to the 4,5-dihydroimidazol-2-ylidene ligand (SIMes, Scheme 1-18) may be used to modulate the solubility of the new complex either protected for organic solubility, or deprotected to increase water-solubility.

Following the publication by Blechert of his work on polymer-supported initiator **29** (Figure 1-13),[77,78] we decided to attach a functional group that would increase the solubility of the initiator in protic solvents at the positions **a** or **b** of the initial ligand (Figure 4-2). The mesityl groups were retained in the design of the ligand, as they are vital for the stabilisation of the carbene.

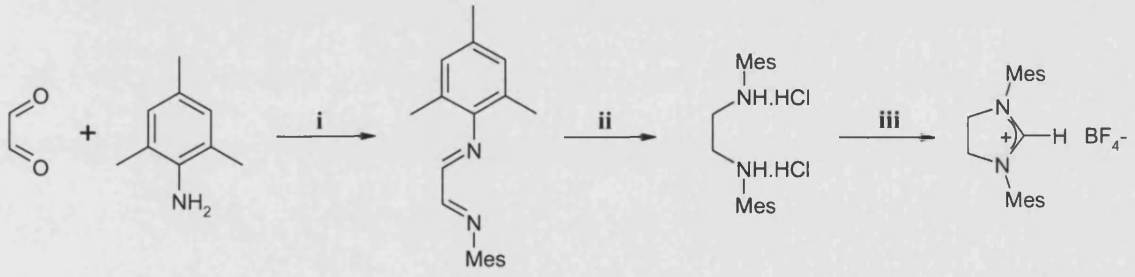


29 **82**

Figure 4-2: Blechert's original second generation polymer-supported catalyst **29** and design of the new ligand for second generation initiators.

4.1 Attempted preparation of *bis*-substituted 1,2-diphenylethanedione

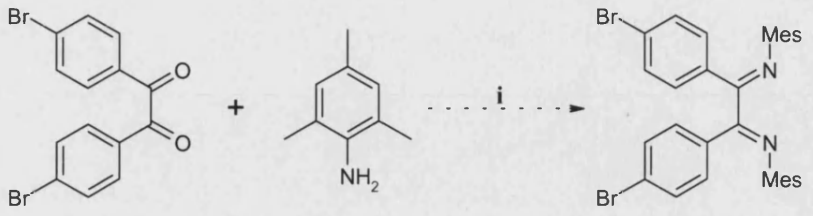
First, Arduengo's method was used for the synthesis of the imidazolylidene ligand (Scheme 4-1).[90]



83 **84** **85** **86** **82.BF$_4$**

Scheme 4-1: Synthesis of 4,5-dihydroimidazol-2-ylidene ligand **82.BF$_4$**: **i**- *n*-propanol, r.t., 16 h, 76 %; **ii**- a) sodium borohydride, anhydrous tetrahydrofuran, r.t., 16 h, b) H_2O, HCl, 5 min, 85 %; **iii**- ammonium tetrafluoroborate, triethyl orthoformate, reflux, 3 h, 66 %.

An attempt was made to synthesise ligand **119** (Scheme 4-2) from 4,4'-dibromobenzil **120** and 2,4,6-trimethylaniline **84** using Arduengo's conditions[90] but the reaction afforded only starting materials, possibly due to the poor solubility of the dibromobenzil. However, when hot tetrahydrofuran was used as solvent, the solubility was increased but the desired 4,4'-dibromobenzil-*bis*-(2,4,6-trimethylphenylamine) imine **119** was not produced.

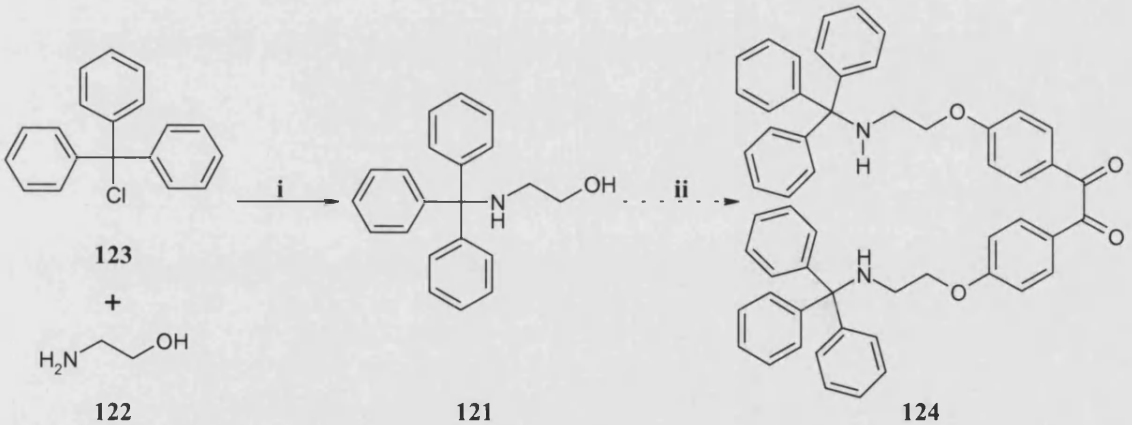


120 **84** **119**

Scheme 4-2: Attempted synthesis of bromophenyl compound **119**: **i**- tetrahydrofuran, reflux, 17 h.

At this stage it was decided to attempt the functionalisation of 4,4'-dibromobenzil prior to the addition of the trimethylaniline to improve its solubility. The substitution of the bromide with a suitably protected amine would increase the solubility of the compound in hydrophobic apolar solvents, while deprotection would increase its solublility in polar solvents.

2-Tritylaminoethanol **121**[107] was produced in 58 % yield following the addition of ethanolamine **122** to tritylchloride **123** in chloroform in the presence of triethylamine (Scheme 4-3). Unfortunately, subsequent addition to dibromobenzil in dimethylacetamide in the presence of sodium hydride[108] at 100 °C again gave only unreacted starting materials.



123 **122** **121** **124**

Scheme 4-3: Attempted synthesis of 2-tritylaminoethanol-substituted compound **124**: **i**- triethylamine, chloroform, r.t., 24 h, 58 %; **ii**- dibromobenzil, sodium hydride, dimethylacetamide, 100 °C, 3 h.

Following unsuccessful substitution of the bromide with 2-tritylamino-ethanol **121**,[107] it was decided to replace the bromide with a *tert*-butoxide group as a trial reaction. The synthesis of *bis*(4-*tert*-butoxyphenyl)ethanedione **125** is a catalytic reaction[109] using

palladium and *bis*(diphenylphosphinyl)ferrocene. Unfortunately, the *bis*(4-*tert*-butoxyphenyl)ethanedione was not produced, possibly due to the quality of sodium *tert*-butoxide used (Scheme 4-4).

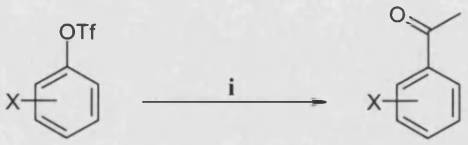
120 **125**

Scheme 4-4: Attempted synthesis of *tert*-butoxy substituted compound **125**: **i**- sodium *tert*-butoxide, $Pd(dba)_2$, *bis*(diphenylphosphinyl)ferrocene, toluene, 100 °C, 20 h.

The use of 4,4'-dibromobenzil as a starting material did not show the desired results and therefore we decided to synthesise our ligand *via* another route.

4.2 Attempted preparation of bis(4-e(thoxycarbonylmethyl)phenyl)ethanedione

The development of a palladium-catalysed method which couples a carbonyl source to a trifluoromethanesulfonate substituent,[110] seemed an attractive way to form a precursor of our target ligand (Scheme 4-5 and Figure 4-3).



Scheme 4-5: Palladium-catalysed reaction coupling trifluoromethanesulfonate substituent to carbon monoxide: i- CO (1 atm.), $SnMe_4$, palladium(II) acetate, 1,3-di(diphenylphosphinyl)propane, triethylamine, dimethylformamide, 60 °C, 2-4 h.

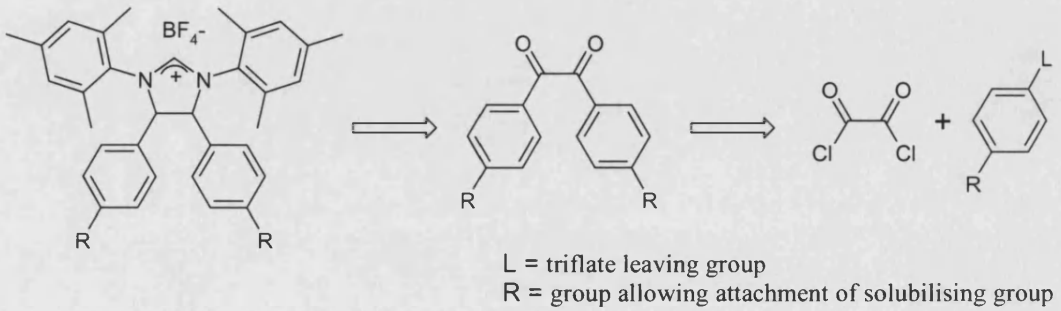
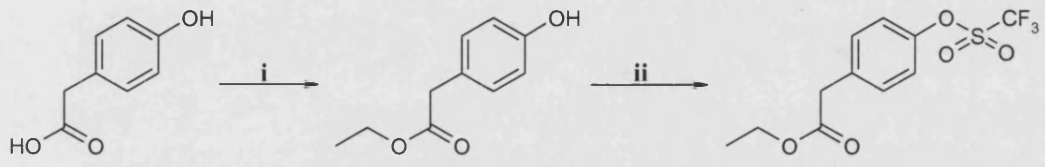


Figure 4-3: Retrosynthetic pathway to form substituted ligand.

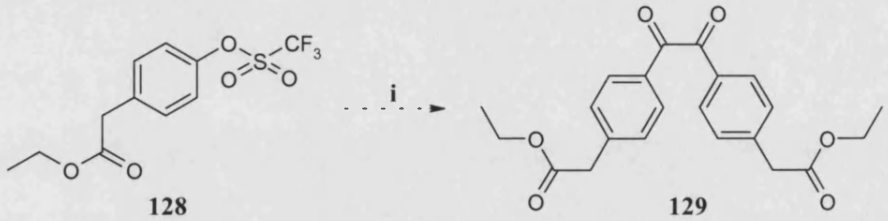
Thus, 4'-hydroxyphenylacetic acid **126** was heated at reflux with sulfuric acid in ethanol for 5 hours, providing ester **127** in 96 % yield (Scheme 4-6). The hydroxyl group was then converted to the trifluoromethanesulfonate ester to provide a good leaving group. Following the Graffner-Nordberg method,[111] trifluoromethanesulfonic anhydride was added to a solution of ester **127** in pyridine and dichloromethane at 0 °C. The reaction mixture was stirred for 1 hour and consecutive washes with water and hydrochloric acid gave 4'-trifluoromethylsulfonyloxyphenyl acetate **128** as a yellow oil in 93 % yield.



126 **127** **128**

Scheme 4-6: Synthesis of triflate ester **128**: **i**- sulfuric acid, ethanol, reflux, 5 h, 96 %; **ii**- trifluromethane sulfonic anhydride, pyridine, dichloromethane, 1 h, 93 %.

Nitrogen was bubbled for 30 minutes at room temperature through a stirred solution of triflic compound **128** in triethylamine and dimethylformamide.[110] Oxalyl chloride was then added dropwise and after 15 minutes palladium (II) acetate and 1,3-*bis*(diphenylphosphinyl)propane were added to the reaction mixture which was heated at 60 °C for 17 hours. After filtration through Celite and work up, the reaction mixture was analysed showing that only starting material was present (Scheme 4-7).



128 **129**

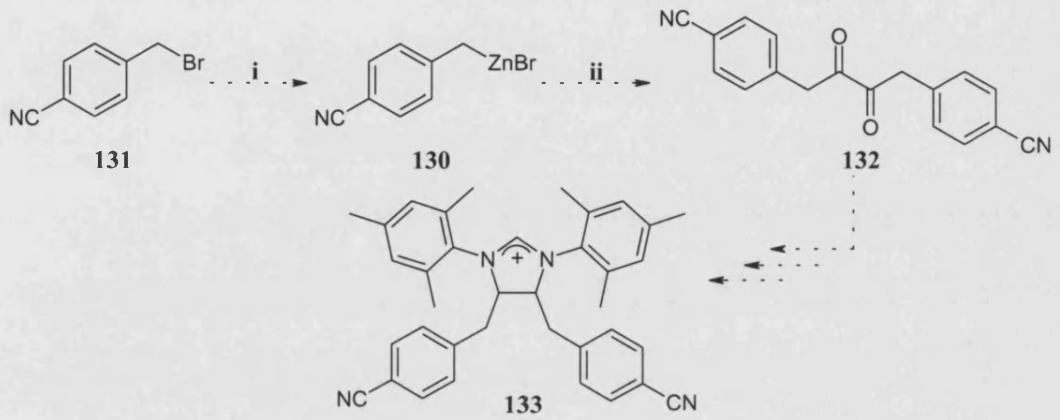
Scheme 4-7: Attempted synthesis of substituted dione **112**: **i**- oxalyl chloride **83** in dichloromethane (2 M), triethylamine, 1,3-*bis*(diphenylphosphinyl)propane, palladium(II) acetate, dimethylformamide, 17 h, 60 °C.

4.3 Attempted preparation of 1,2-di(4-cyanobenzyl)ethanedione

The previous methods may have failed due to the poor solubility of the reagents and perhaps due to deactivation of the carbonyl groups caused by conjugation with

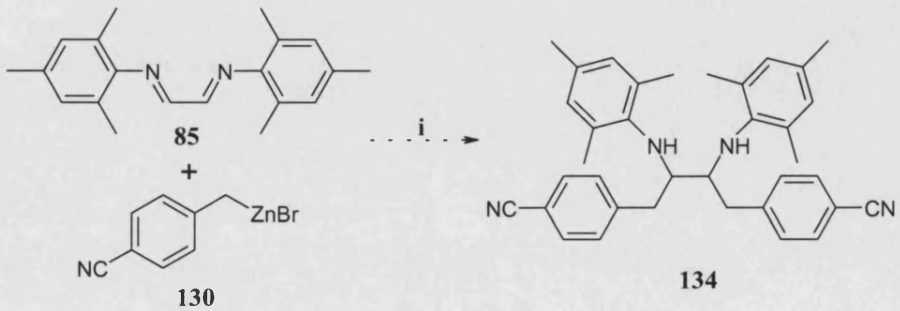
aromatics. We chose to examine benzyl substituents in an attempt to obtain more flexible compounds that may be more soluble.

Zincate compound **130** was formed from 4-bromophenylacetonitrile **131**,[112] and was combined with oxalyl chloride,[113] in the presence of copper(I) bromide and lithium bromide to form intermediate **132** that could be used as a precusor for imidazolylidene analogue **133** (Scheme 4-8).



Scheme 4-8: Attempted synthesis of 1,2-di(4-cyanobenzyl)ethanedione **132**: **i**- zinc, 1,2-dibromoethane, chloro-trimethylsilane, tetrahydrofuran, 30 min, 0 °C-r.t.; **ii**- lithium bromide, copper(I) bromide, oxalyl chloride in dichloromethane (2 M), 15 min, 0 °C.

Unfortunately, the reaction did not produce the desired dione and repeating the reaction with commercially available α-zincbromo-*p*-tolunitrile, used directly in the second step of the synthesis, gave the same result. The moisture-sensitivity of oxalyl chloride could limit the reaction, therefore a more direct reaction with the zincate was performed on the more stable 1,2-*bis*(2,4,6-trimethylphenylimino)ethane **85** (Scheme 4-9), but this failed to produce the desired compound **134**.

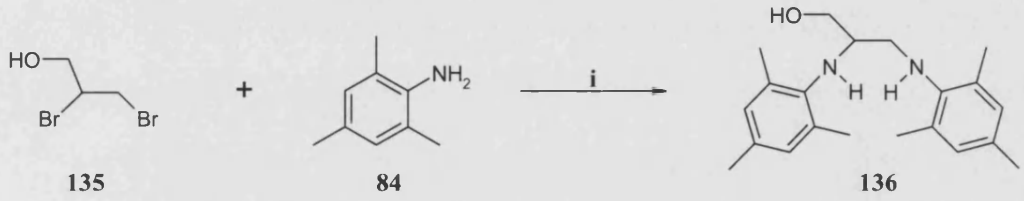


Scheme 4-9: Attempted preparation of 1,2-*bis*(2,4,6-trimethylphenylimino)-1,2-di(4-cyanobenzyl)ethane **134** : **i**- lithium bromide, copper(I) bromide, oxalyl chloride in dichloromethane (2 M), 15 min, 0 °C.

Due to its sensitivity to air and water, the zincate reagent was analysed by NMR spectroscopy showing decomposition towards 4-cyanotoluene, probably explaining the unsuccessful results. The instability of α-zincbromo-*p*-tolunitrile limits the scope of this reaction and led us to investigate an alternative route.

4.4 Synthesis of mono-substituted imidazolylidene ligands

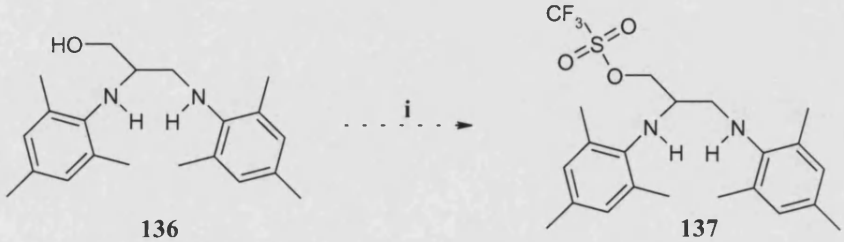
By following the synthesis of a silica-based heterogeneous second generation catalyst,[114] we were able to insert a functional group onto the imidazolylidene ligand. 2,3-Dibromopropanol **135** and 2,4,6-trimethylaniline **84** were heated at reflux for 24 hours forming a solid, which was then dissolved in dichloromethane and sodium hydroxide (15 % aq) (Scheme 4-10). The residue was purified by flash chromatography to afford **136** in 79 % yield as a white solid.



135 **84** **136**

Scheme 4-10: Synthesis of *N,N'*-dimesityl-2,3-diamino-1-propanol **136**: reflux, 24 h, 79 %.

The hydroxyl group was then converted to the triflate, a good leaving group that would allow the introduction of a hydrophilic moiety to the ligand. Addition of trifluoromethanesulfonic anhydride to a solution of **136** in pyridine and dichloromethane at 0 °C,[44] led to a yellow oil after three hours of reaction and aqueous work-up. However, purification by flash chromatography was unsuccessful as the mixture stuck to both silica and glassware (Scheme 4-11).

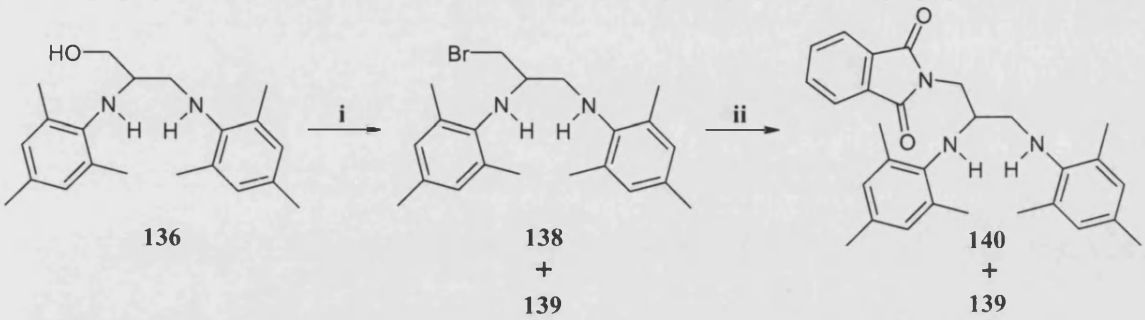


136 **137**

Scheme 4-11: Attempted preparation of triflic compound **137**: **i**- trifluoromethane sulfonic anhydride, pyridine, dichloromethane, 3 h, 0 °C-r.t..

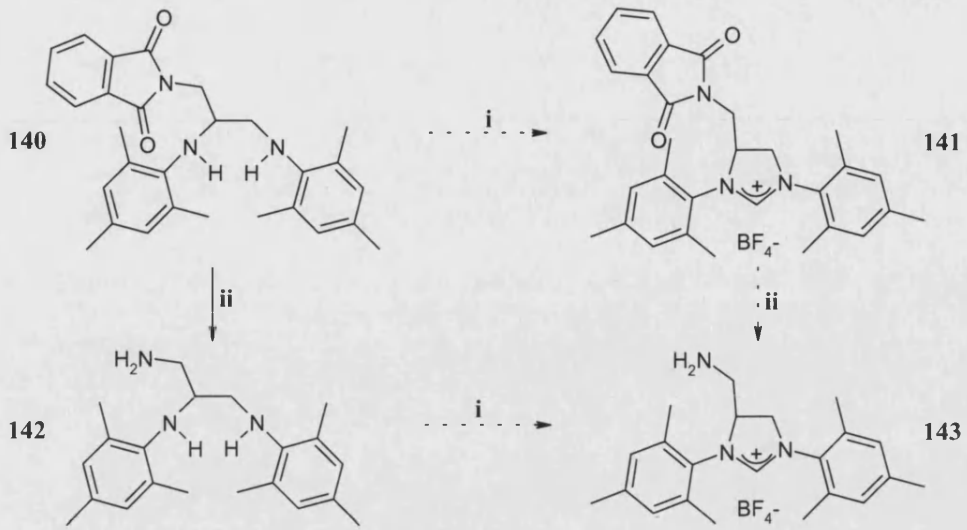
The difficulty of handling or purifying triflate **137** led to consideration of another route. Bromination of the alcohol **136** using triphenylphosphine, pyridine and carbon

tetrabromide afforded a mixture of compounds **138** and an unknown compound **139** with the same R_f (Scheme 4-12). The mixture of compounds was then treated with potassium phthalimide in dimethylformamide and heated at 80 ºC, giving compound **140** in a purified yield of 61 % over two steps. This second step confirmed the presence of a secondary product **139**, which remained unchanged (R_fs 0.70:0.46, **139**:**140**), however this material could not be identified from the isolated material (NMR analysis showed a messy spectrum).



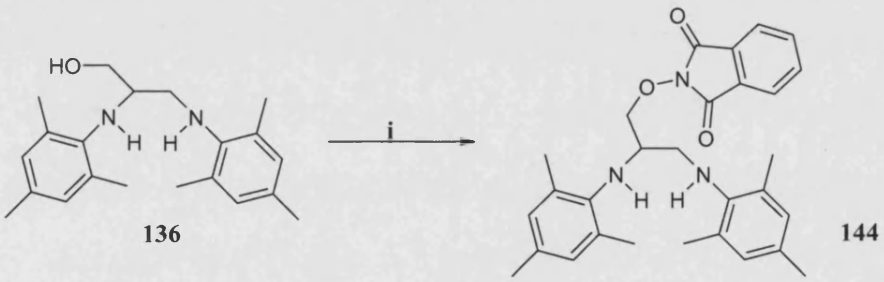
Scheme 4-12: Synthesis of *N*,*N*'-dimesityl-2,3-diamino-1-phthalimido-propane **140**: **i**- triphenylphosphine, carbon tetrabromide, pyridine, tetrahydrofuran, 17 h; **ii**- potassium phthalamide, 24 h, 80 ºC, 61 % over two steps.

Intermediate **140** was then subjected to the same procedure as the original imidazolylidene ligand, heating it at reflux in the presence of ammonium tetrafluoroborate, triethyl orthoformate, for 3 hours (Arduengo's method).[90] Unfortunately, the reaction did not produce the expected compound **141** (Scheme 4-13), apparently due to cleavage of the phthalimide from the *N*,*N*'-dimesityl-2,3-diamino-propane, suggested by the loss of aromatic protons in NMR spectra. Another option was to deprotect the phthalimide group to an amine, and try to close the ring, thus deprotected compound **142** was produced in quantitative yield and subjected to ammonium tetrafluorobarate, triethyl orthoformate, for 3 hours. The presence of the free amine was problematic, presumably providing a competitive reaction for the closing of the immidazolylidene ring.



Scheme 4-13: Attempted of synthesis of ligand **141** or **143**: **i**- ammonium tetrafluoroborate, triethyl orthoformate, reflux, 3 h; **ii**- hydrazine hydrate, ethanol, 120 ºC, 2 h (98 %, **142**).

An analogue of **140** was produced by subjecting the alcohol **136** to Mitsunobu[115] reaction by slow addition of the coupling reagent, diethyl azodicarboxylate, to *N*-hydroxyphthalimide in tetrahydrofuran, providing the product **144** after purification, in 40 % yield (Scheme 4-14).



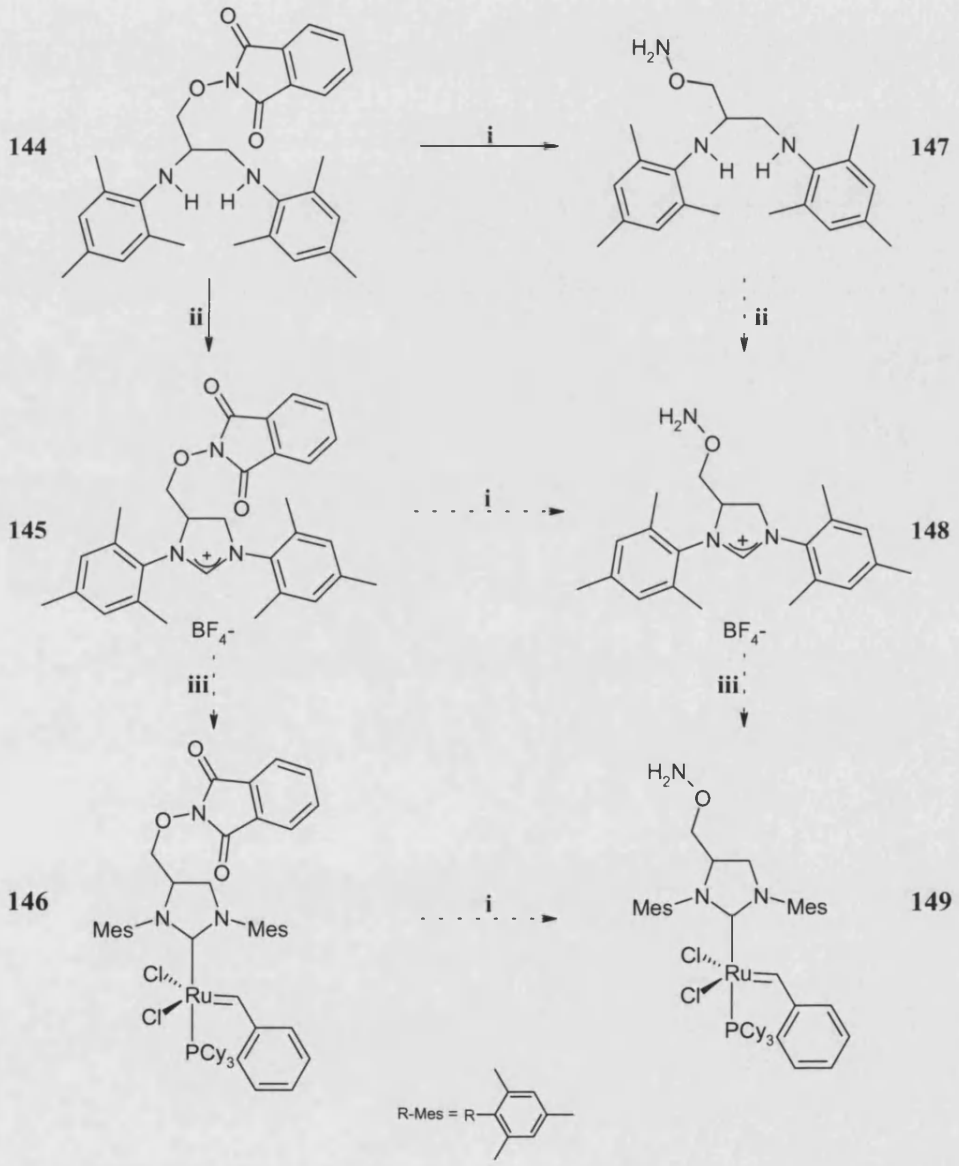
Scheme 4-14: Synthesis of protected amino compound **125**: **i**- *N*-hydroxyphthalimide, diethyl azodicarboxylate, triphenylphosphine, anhydrous tetrahydrofuran, r.t., 24 h, 40 %.

Intermediate **144** was subjected to the same procedure used to close the initial *N*-heterocyclic ring **82** by heating it in the presence of ammonium tetrafluoroborate and triethyl orthoformate, for 3 hours (Arduengo's method),[90] affording the new ligand **145** in 89 % yield (Scheme 4-15).

Reaction of imidazolylidene ligands with Grubbs catalyst normally proceeds by deprotonation of the ligand **82**, as its anion is soluble in hexane allowing the reaction to

proceed. Unfortunately, the modified ligand was not soluble under these conditions and did not lead to modification of Grubbs catalyst.

The literature shows that the loading of imidazolylidene ligands can be performed in solvents other than hexane.[46,103,104,116] Therefore, the reactions were carried out using anhydrous degassed tetrahydrofuran, toluene and hexane with potassium *tert*-pentylate and potassium *tert*-butoxide as bases, in parallel under argon. Unfortunately, the ligand was only partially soluble in these solvents and initiator **146** was not produced (Scheme 4-15).



Scheme 4-15: Attempted synthesis of second generation analogues **146** and **149**: **i**- hydrazine hydrate, ethanol, 120 °C, 2 h, (**147**, 92 %); **ii**- ammonium tetrafluoroborate, triethyl orthoformate, reflux, 3 h, (**145**, 89 %); **iii**- a) potassium *tert*-pentylate in toluene (1.7 M), degassed hexane, r.t., 1.5 h, b) Grubbs catalyst **3**, degassed hexane, 60 °C, 2 h.

Deprotection of the ligand may improve the solubility and consequently, the phthalimide group of compound **144** was cleaved using hydrazine hydrate, affording amine **147** in 92 % yield. Unfortunately, reaction with ammonium tetrafluorobarate and triethyl orthoformate did not close the heterocyclic ring, probably due to the reactive free amine. It was then decided to deprotect the imidazolylidene intermediate **147** in the presence of hydrazine hydrate in ethanol in order to change the solubility of the ligand, but aminoxy compound **148** was not produced and therefore could not be loaded onto Grubbs catalyst **3**.

4.5 Summary

The synthesis of novel imidazolylidene ligand towards second generation catalysts that are soluble in polar solvents is described. Initial routes, *via* the glyoxal moiety were unsuccessful, therefore another route was followed leading to *N*,*N*'-dimesityl-2,3-diamino-1-propanol **136**. This was successfully substituted with *N*-hydroxyphthalimide, and the imidazole ring closed following Arduengo's method. Unfortunately, attempts to form novel second generation catalysts were unsuccessful due to poor solubility in various solvents (hexane, tetrahydrofuran and toluene). The problem of solubility of our ligand was not resolved and further investigation was not possible due to lack of time. The study of different functional and protecting groups would have given us a better understanding of the problems encountered.

5.0 Towards the synthesis of a library of fructose transport inhibitors

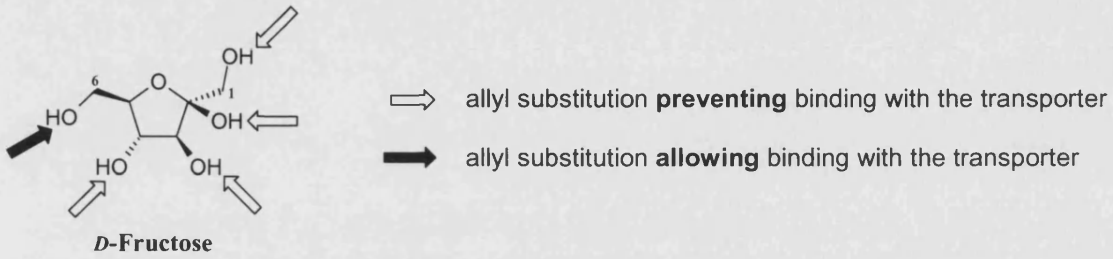
In order to test our initiators, we set out to synthesise fructose analogues that could be tested as chemical probes of the fructose transporter GLUT5. This would provide a test of the utility of our initiators and a useful model to further develop the olefin metathesis initiators towards the goal of performing olefin metathesis in the presence of a biological target.

5.1 Fructose transport inhibitors

Glucose transport is facilitated by proteins from the GLUT family that belong to a superfamily of 12 transmembrane transporters. The first class, GLUTs 1-4, are primarily glucose transporters with distinct tissue distributions. The second class, GLUT5 and two new members, GLUTs 9 and 11, are fructose transporters. GLUT5 is abundant in spermatozoa (sperm cells utilize fructose in seminal fluid), in intestinal cells, kidneys and substantial levels are also present in muscle tissue. The expression of GLUT5 in human muscle has been linked to the ability of muscle to use fructose for glycolysis and glycogenesis.[117] Interestingly, fructose transport mediated by GLUT5 is insensitive to inhibition by cytochalasin B, a well-characterised inhibitor of glucose transporters, suggesting that glucose and fructose are unlikely to share a common transporter.[118]

Characterisation of glucose transporters is difficult because they are very large membrane bound proteins, consequently, their crystallography is difficult. The development of fructose transport inhibitors may help to elucidate the structural motifs present in the transporters binding domain, therefore improving our understanding of the transport of fructose into cells. Further modifications to these inhibitors may allow the attachment of a photo-affinity label, which, upon binding to the transporter, could be activated forming a covalent bond with GLUT5. The binding domain of the transporter could be isolated using an enzyme digest followed by purification to give the inhibitor-binding domain complex. This could be subjected to a series of analysis to determine the amino acid sequence present in the active site, thus improving understanding of this biologically important transporter.

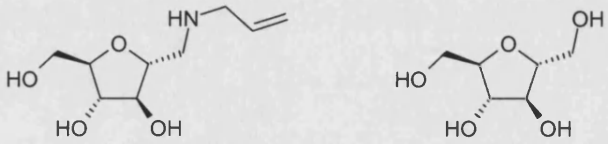
A study[119] of the fructose transport GLUT5 shows that it can intercept *D*-fructose in both the furanose and pyranose forms suggesting that the arrangement of hydroxyls on the positions 1, 2, 3 and 4 of the ring and the ring oxygen are essentially the same in these two forms. Allyl substitutions at positions 1, 2, 3 and 4 prevent the binding between the substrate and fructose transporter. However, it was found that incorporation of the allyl group at position 6 of *D*-fructofuranose increases binding with GLUT5.



***D*-Fructose**

Figure 5-1: Structural study of GLUT5, *via* allylation of alcohol functionalities of *D*-fructose.

In order to explore the spatial restrictions around the binding site of *D*-frutose on GLUT5 and other *D*-frutose transporters that are present at the surface of target cells, Holman and co-workers synthesised a range of *D*-fructose analogues such as 1-allylamine (**150**) and 2,5-anhydro-*D*-mannitol **151** (Figure 5-2) which were recognised as potential ligands for GLUT5.

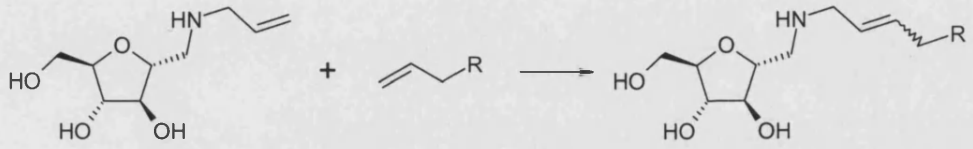


150 **151**

Figure 5-2: 1-Prop-2-enylamino-2,5-anhydro-*D*-mannitol **150** and 2,5-anhydro-*D*-mannitol **151**.

2,5–Anhydro-*D*-mannitol **151** provides a C-glucoside analogue of the protected fructose in the furanose form and can be used as a stable compound with which to probe the substrate specificity of GLUT5. The substitution of a secondary amine group to replace the hydroxyl group on C-6 (or C-1, as the molecule is symmetrical) from 2,5–anhydro-*D*-mannitol results in compounds of high affinity (~ 10 times) relative to *D*-fructose. Therefore, 1-allylamino-2,5-anhydro-*D*-mannitol **150** was synthesised and found to be a better inhibitor than 2,5-anhydro-*D*-mannitol.[120]

Claustre and co-workers developed a synthesis of 2,5-anhydro-*D*-mannose (**152**, Scheme 5-2), a convenient precursor, which also proved to be an efficient fructose transport inhibitor and has the basic structure of all the analogues we wished to synthesise.[121] Attachment of hydrophobic group to C-6 of 2,5–anhydro-*D*-mannitol improved binding of the inhibitor with GLUT5. It was thus decided to attempt the synthesis of a small library of GLUT5 inhibitors by attaching a variety of groups to 1-allylamino-2,5–anhydro-*D*-mannitol *via* olefin metathesis in order to study the interaction of these molecules with GLUT5 (Scheme 5-1).



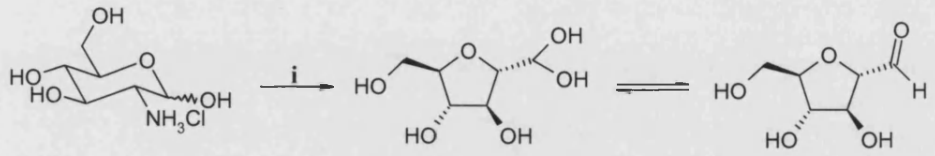
150

Scheme 5-1: Olefin cross-metathesis leading to possible fructose transport inhibitors.

5.2 Synthesis of possible inhibitors of *D*-fructose transporter GLUT5

5.2.1 Synthesis of allylamino analogues of *D*-fructose

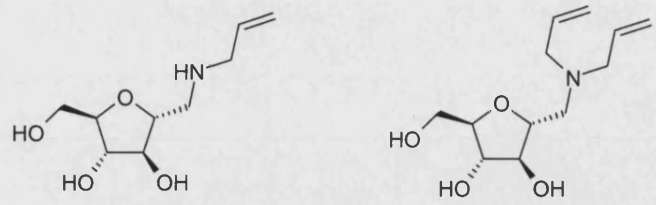
Following the Claustre method (modified from Horton and Philips), 2,5-anhydro-*D*-mannose **152** was prepared by nitrous acid deamination of 2-amino-2-deoxy-*D*-glucose hydrochloride **153**. [121-123] Addition of acidic resin to an aqueous solution of sodium nitrate and glucosamine was stirred at mutarotational equilibrium. The reaction was filtered and neutralised using anion exchange resin giving aldehyde **152** after filtration and concentration as a pale yellow solid.



153 **152**

Scheme 5-2: Synthesis of 2,5-anhydro-*D*-mannose **152**: **i**- a) sodium nitrite, Amberlite IR-120 (H^+), 0-5 °C, 4 h, b) Dowex 1 x 8-50 (OH^-), 80 %.

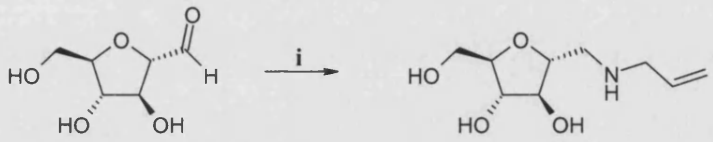
1-Allylamino-2,5-anhydro-*D*-mannitol **150** has been previously synthesised and proved to be a better GLUT5 inhibitor than 2,5-anhydro-*D*-mannose **152**. Therefore, an attempt was made to synthesise similar substrates such as 1-diallylamino-2,5-anhydro-*D*-mannitol **154**, with the aim of attaching various groups *via* olefin metathesis allowing further investigation of GLUT5.[124]



150 **154**

Figure 5-3: Example of fructose amino derivatives.

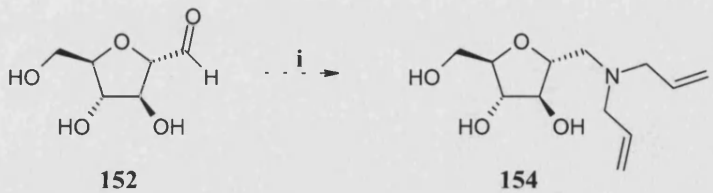
Allylamino sugar **150** was prepared by reductive amination (Scheme 5-3). Purification was achieved first by adsorption onto acidic Dowex resin in order to capture the amino-compound. Then the resin was rinsed with methanol to remove the excess reagent and starting material and was finally washed with methanolic ammonia to free the amino sugar. Subsequent purification by column chromatography furnished compound **150** in a yield of 30 %.



152 **150**

Scheme 5-3: Synthesis of 1-allylamino-2,5-anhydro-*D*-mannitol **150**: **i**- sodium cyanoborohydride, allylamine, methanol, r.t., 18 h, 30 %.

Reductive amination of **152** with diallylamine was carried out using sodium cyanoborohydride, in methanol (Scheme 5-4).[121,123] Pre-purification was achieved by adsorption onto acidic Dowex followed by washing with methanol to remove excess sodium cyanoborohydride. Unfortunately, the desired amino sugar **154**, could not be purified by subsequent column chromatography.

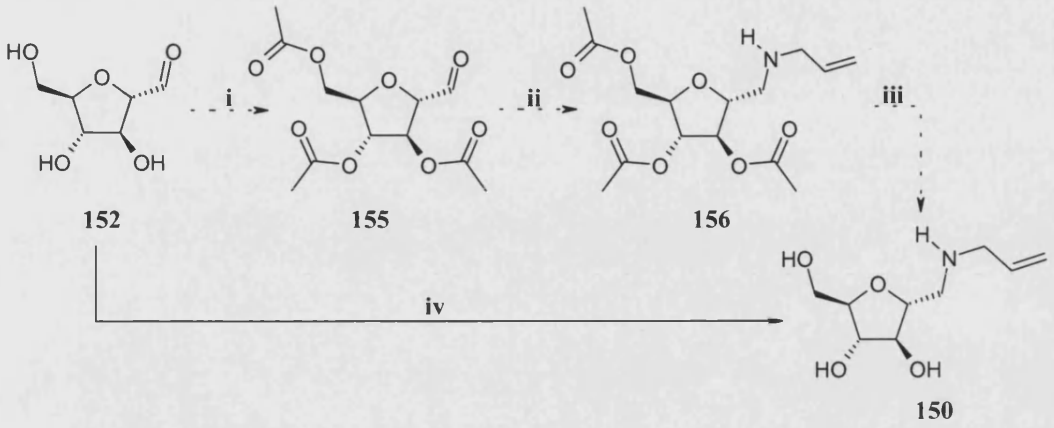


152 **154**

Scheme 5-4: Synthesis of 1-diallylamino-2,5-anhydro-*D*-mannitol **154**: **i**- sodium cyanoborohydride, diallylamine, methanol, r.t., 18 h.

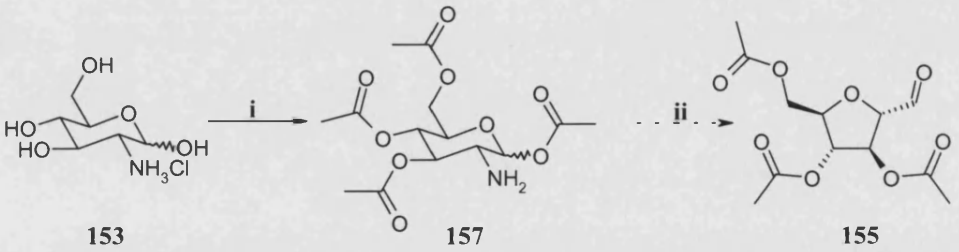
Purification of the allylamino sugar **150** was problematic and yields were poorly reproducible not least because of its polarity. As an alternative route, protection of the hydroxyl groups of 2,5-anhydro-*D*-mannose **152** using acetic anhydride and pyridine

would afford **155** which could be more easily purified. NMR analysis of the reaction product did not show the presence of the expected compound **155** (Scheme 5-5).



Scheme 5-5: Attempted synthesis of 1-allylamino-2,5-anhydro-*D*-mannose **150**: **i**- acetic anhydride, pyridine, 50 °C, 20 h; **ii**- allylamine, dichloromethane; **iii** sodium methoxide, methanol; **iv**- sodium cyanoborohydride, allylamine, methanol, r.t, 18 h.

Following the method developed by Horton *et al.*,[123] treatment of 2-amino-2-deoxy-*D*-glucose hydrochloride **153** with a large excess of acetic anhydride in pyridine afforded the protected sugar **157** (81 % yield) as a white solid after purification (Scheme 5-6). Unfortunately, the attempt to effect deamination using sodium nitrite with acidic resin was unsuccessful, possibly due to the poor water-solubility of the protected sugar **137** compared to the sugar **152** used initially.

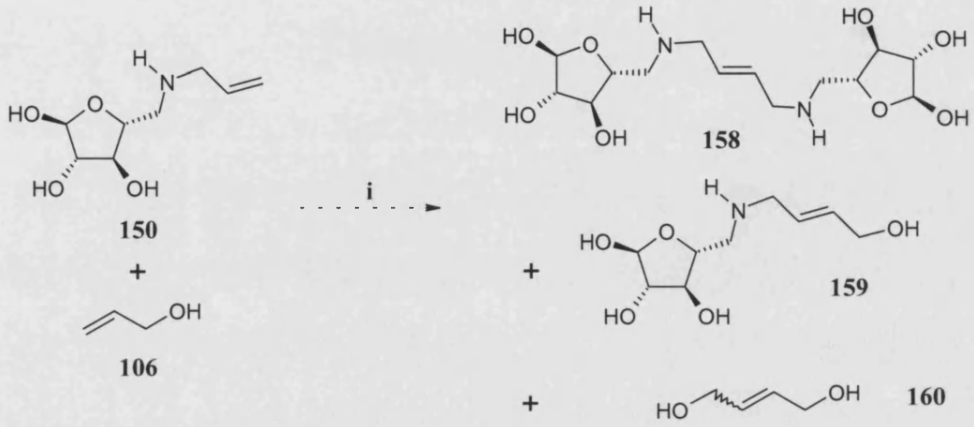


Scheme 5-6: Attempted synthesis of protected 2,5-anhydro-*D*-mannose **155**: **i**- acetic anhydride, pyridine, r.t., 16 h, 90 %; **ii**- sodium nitrite, Amberlite IR-120 (H^+), methanol, 0-5 °C, 4 h, Dowex 1x8-50 (OH^-).

Finally, reductive amination of **152** was performed as previously, using allylamine and the purification was carried out in two steps. The reaction mixture was first columned using a gradient of methanol and dichloromethane (1:4) affording a pale yellow oil which was then crystallised using a small amount of methanol and addition of ether giving 1-allylamino-2,5-anhydro-*D*-mannose **150** as a white solid in 50 % yield.

5.2.2 Attempted cross-metathesis of allylamino analogues

The allylamino sugar **150** was subjected to olefin-cross metathesis with allyl alcohol in the presence of second generation polymer-supported catalysts **88**, **104** (polystyrene and PEGA resin respectively) and Grubbs second generation **7** (Scheme 5-7). Various solvents were used, including D_2O, methanol, and dichloromethane (in the presence of BSA (*bis*-trimethylsilylacetamide) which protects the hydroxyl groups and increase the solubility. Unfortunately, cross-coupling did not produced the expected compouinds **158**, **159** and **160**, and the amine was recovered unchanged.

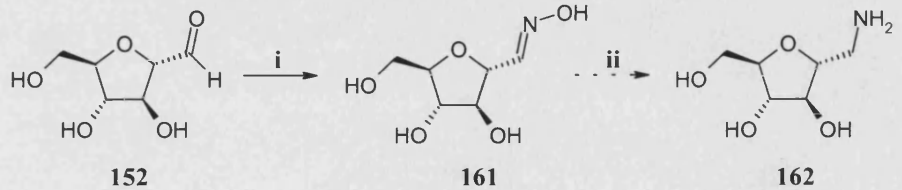


Scheme 5-7: Attempted olefin-cross metathesis of 1-allyl-2,5-anhydro-*D*-mannose **150** with allyl alcohol **106**: i- **88**, **104** or **7**, solvent, 1.5 h.

Following the unsuccessful olefin metathesis of the allylamino sugar **150**, other methods were considered to introduce the allyl functionality, necessary for cross-metathesis, on the sugar moiety.

5.2.3 Synthesis of oxime sugars as precursors for cross-metathesis

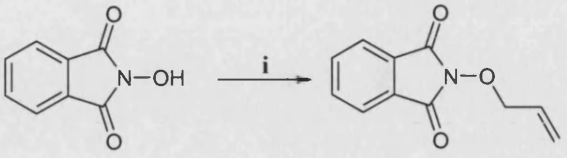
Following Clautre's method,[121] oxime **161** was formed from aldehyde **152** and hydroxylamine chloride in methanol in a yield of 69 % with no need for further purification (Scheme 5-8). Subsequent hydrogenolysis using formic acid in methanol and Pd/C, did not produce the desired amino sugar **162**.



Scheme 5-8: Attempted synthesis of amino sugar **142**: **i**- hydroxylammonium chloride, sodium acetate, methanol, r.t., 18 h, 69 %; **ii**- formic acid in methanol (4.4 %), Pd/C 10 %, H_2, 17 h.

The successful synthesis of oxime **161** encouraged the development of a series of substrates by simple addition of aminoxy salts to 2-anhydro-*D*-mannose **152**.

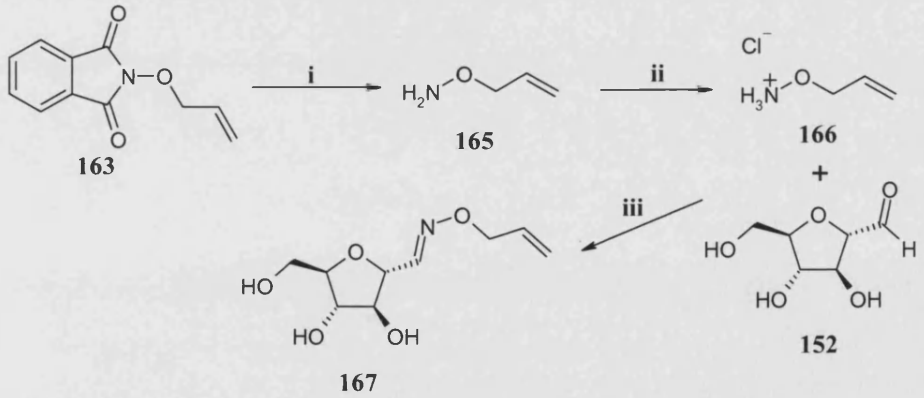
Initially the substituent 2-allyloxy-*iso*-indole-1,3-dione **163** was synthesised following the procedure of Koyama using *N*-hydroxyphthalimide **164** (Scheme 5-9).[125]



164 **163**

Scheme 5-9: Synthesis of allyloxyphthalimide **163**: **i**- sodium hydride, allyl bromide, tetrahydrofuran, 0 °C-r.t., 17 h, 55 %.

Cleavage of the phthalimide group using hydrazine hydrate in ethanol under reflux was performed and the resulting residue subjected to aqueous work-up. The product **165** is highly volatile, therefore extraction with ether was followed by addition of aqueous hydrochloric acid in order to afford *O*-prop-2-enylhydroxylammonium chloride **166** in 54 % yield (Scheme 5-10). This salt was then directly used in the addition with 2,5-anhydro-*D*-mannose **152** in the presence of pyridine, producing the desired oxime **167** after purification in 41 % yield.



163 **165** **166** + **152** **167**

Scheme 5-10: Synthesis of allyl oxime sugar **167**: **i**- hydrazine hydrate, ethanol, reflux, 2 h, **ii**- Hydrochloric acid (1 M) (54 % over two steps); **iii**- pyridine, dimethylformamide, r.t., 24 h, 41 %.

Production of prop-2-enyloxyammonium chloride salt **166** was disappointing, presumably due to the difficulty in affording dry salt. A range of sources of dry hydrochloric acid in volatile solvents was therefore tested to attempt to improve the yield (Table 5-1).

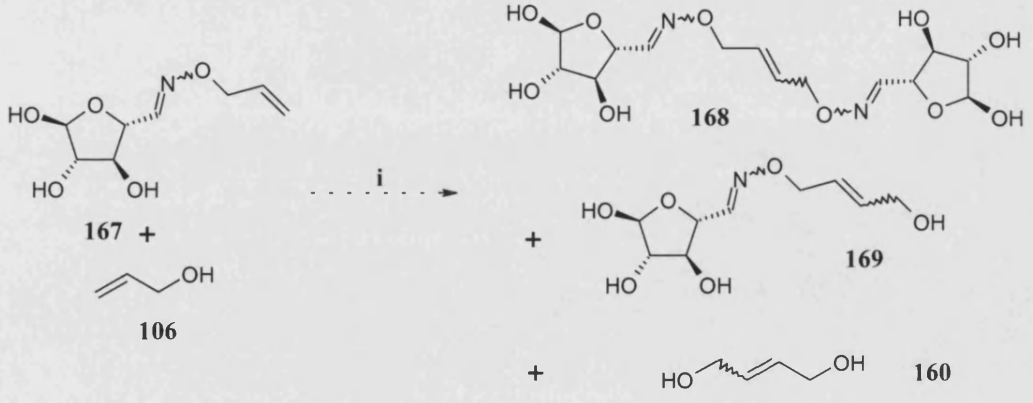
Entry	Solvent	Concentration (mol/L)	Yield (%)
1	Water	**1**	**54**
2	Ether	**1**	**64**
3	Dioxane	**4**	**30**
4	Methanol	**1.25**	**84**

Table 5-1: Effect of hydrochloric acid in different solvents in the formation of **166** (scheme 4-24).

Satisfyingly, hydrogen chloric in methanol provided the salt **166** in a good of 84 %.

5.2.4 Attempted olefin cross-metathesis of oximes towards GLUT5 inhibitors

Substrate **167** was designed to be used for olefin-cross metathesis with various allyl compounds in order to afford products that would be tested as potential *D*-fructose transport inhibitors. Allyl alcohol **106** was chosen as a test substrate for addition to **167** in all the reactions as it is soluble in polar solvents and it was available in large quantities (4 eq used) (Scheme 5-11). The first reaction was performed with second generation PEGA-supported initiator **104**, in methanol, at 45 °C. After 90 minutes, the reaction mixture was filtered and concentrated for later analysis by NMR. Unfortunately, the ^{1}H NMR spectrum showed no conversion of the oxime sugar **167** to the corresponding cross-metathesis products (**168**, **169** and **160**) with only starting material and the formation of compound **160** being detected.



Scheme 5-11: Olefin cross-metathesis of substrate **167** with allyl alcohol **106**; i-catalyst **104**, methanol, 45 °C, 90 minutes.

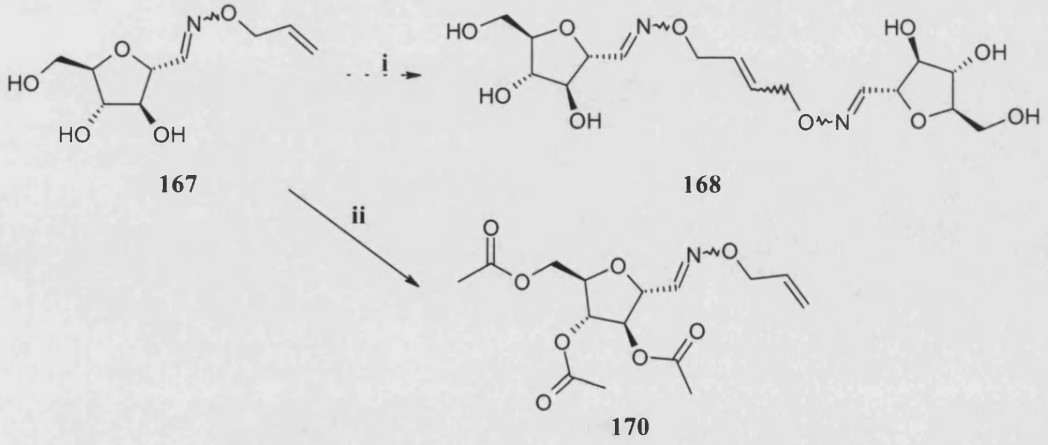
The reaction was performed using various solvents (methanol, D_2O, dichloromethane), initiators (**88**, **104** and **7**), and time periods (90 minutes to 24 hours), but all conditions

proved unsuccessful. Protection of the hydroxyl groups of the substrates using BSA in order to increase solubility also failed to encourage the reaction.

The efficiency of both supported initiators was then tested in ring-closing diallyl carbamate **54** (scheme 3-13) to discount possible decomposition that may have decreased their catalytic activity. Both polymer-supported initiators **88** and **104** converted **54** in 97 % yield, showing that their efficiency was not the cause of the poor results.

To eliminate the effect of the polymer support, second generation Grubbs catalyst **7** was used to catalyse the reaction in methanol or in dichloromethane using BSA to solubilise the sugar in non-protic solvents. Unfortunately, ^{1}H NMR analysis showed only the presence of starting material **167** and compound **160** for both solvents. The literature shows that sugars have been used successfully in olefin cross-metathesis, however these reactions have been carried out using protected sugars[126,127] in solvents such as dichloromethane.

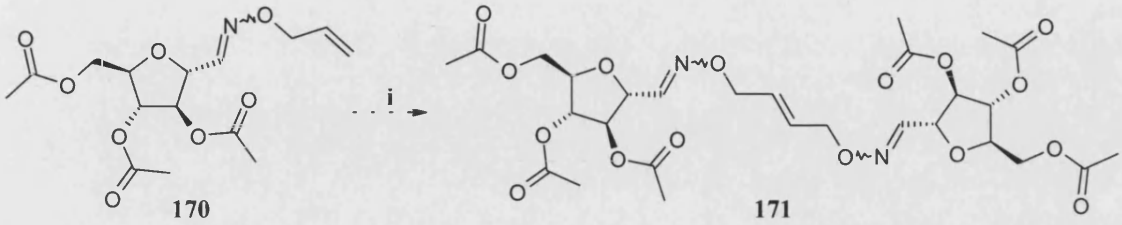
To simplify this study, homo-coupling of the sugar **167** alone was carried out but no conversion to **168** was observed by ^{1}H NMR spectroscopy. The problem of solubility was considered and the allyl oxime sugar **167** was protected in order to carry out the reaction in chlorinated solvents. Each hydroxyl group was modified with an acetate protecting group using acetic anhydride in pyridine which afforded **170** as a yellow oil (92 % yield) (Scheme 5-12).



167 **168** **170**

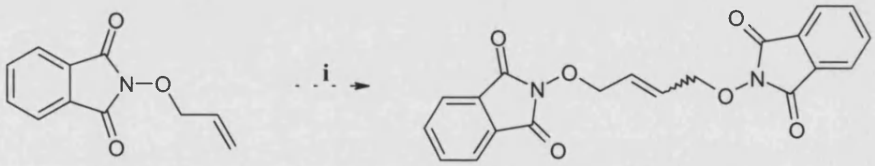
Scheme 5-12: Olefin cross-metathesis of allyl oxime **167** and its protection; **i**- **104** or **7**, $CDCl_3$, 45 °C, 90 minutes; **ii**- acetic anhydride, pyridine, r.t., 16 h, 92 %.

The olefin-cross metathesis reaction of **170** was carried out in an NMR tube, in deuterated chloroform and was monitored after 2, 5, 22 and 24 hours, but the ^{1}H NMR spectra showed no conversion to **171**, suggesting that solubility might not be the problem (Scheme 5-13).



Scheme 5-13: Olefin cross-metathesis of protected sugar **170**: **i**- Grubbs second generation catalyst **7**, $CDCl_3$, 45 °C, 1.5, 2, 5, 22 and 24 h.

It was considered that the oxime could be responsible for the poor results. This concept was tested using precursor allyloxyphthalimide **163** (used in the synthesis of allyl oxime sugar **167**) in olefin-cross metathesis using second generation Grubbs catalyst **7** in deuterated chloroform (or dichloromethane) (Scheme 5-14). No conversion to **172** was observed when the crude mixture was analysed by ^{1}H NMR suggesting that this functional arrangement could therefore be inhibiting the cross-metathesis reaction.

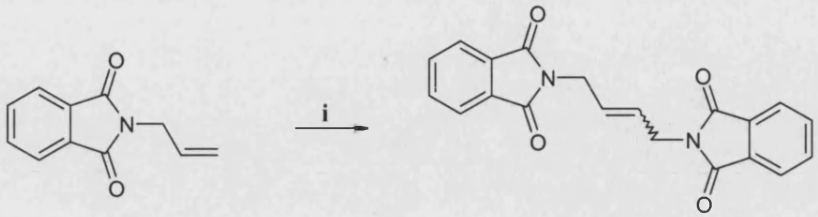


Scheme 5-14: Olefin cross metathesis of precursor **163**: **i**- Grubbs second generation catalyst **7**, $CDCl_3$, r.t., 24 h.

To confirm this hypothesis, allyl phthalimide was synthesised to be tested in olefin cross-metathesis. To potassium phthalimide **173** in anhydrous dimethylformamide was added allyl bromide and the reaction was then stirred overnight at 50 °C. Purification by flash chromatography afforded allyl phthalimide **174** in 94 % yield (Scheme 5-15).

Scheme 5-15: Synthesis of allylphthalimide **174**: **i**- allyl bromide, dimethylformamide, 50 °C, 17 h, 94 %.

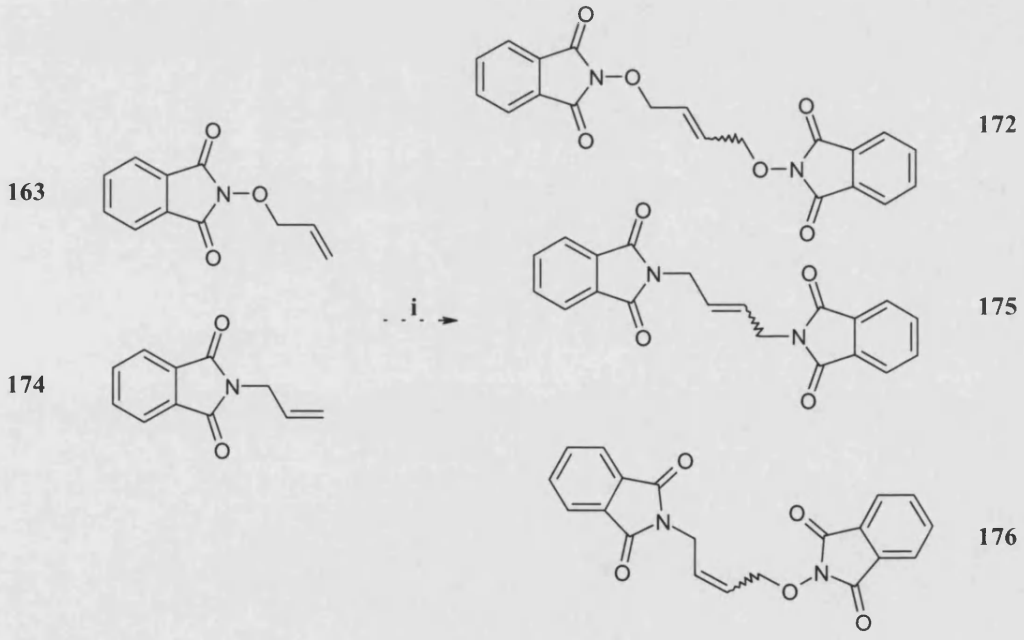
Olefin-cross metathesis was carried out in an NMR tube in deuterated chloroform with second generation Grubbs catalyst **7** (Scheme 5-16). After 5 hours, 50 % of compound **174** had been converted to **175** determined by ^{1}H NMR (the same yield was observed after 19 hours).



174 **175**

Scheme 5-16: Olefin cross-metathesis of substrate **174**; **i**- second generation Grubbs catalysts **7**, $CDCl_3$, r.t., 19 h, 50 %.

N-allyloxyphthalimide and *N*-allylphthalimide were next tested together in olefin-cross metathesis in order to determine whether compound **163** inhibits the ruthenium catalyst. The reaction was carried out in an NMR tube in deuterated chloroform at 45 °C with the ^{1}H NMR spectra showing no cross-metathesis products (**172**, **175** and**176**, Scheme 5-17) formed.



Scheme 5-17: Olefin cross-metathesis of substrates **163** and **174**; **i**- second generation Grubbs catalysts **7**, $CDCl_3$, 45 °C, 24 h.

It is possible that allyoxy phthalimide forms a complex with the ruthenium (Figure 5-4), dramatically reducing its efficiency in olefin cross-metathesis. This theory was

confirmed by the fact that allylphthalimide reacts in olefin cross-metathesis, but when mixed with allyoxyphthalimide no conversion is observed.

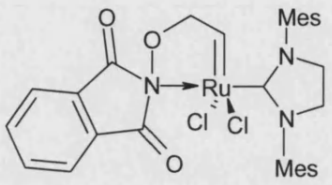
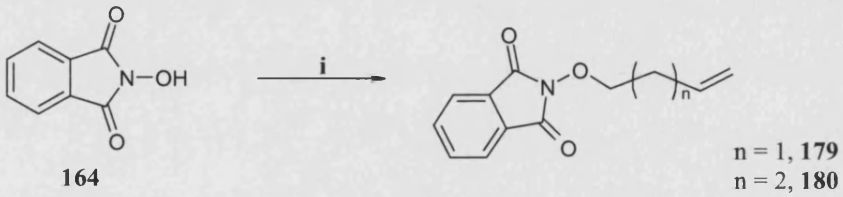


Figure 5-4: Possible inhibition complex.

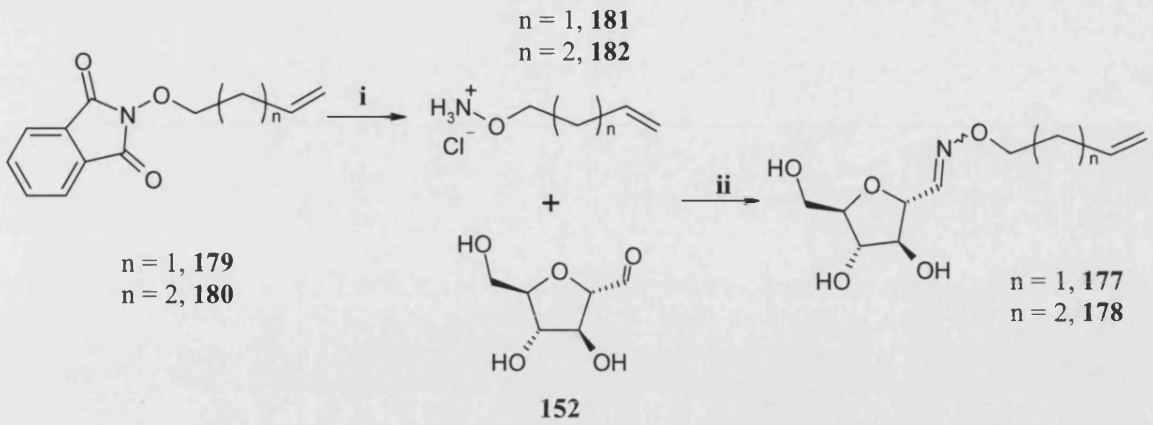
In order to avoid the formation of such a complex, the chain supporting the terminal alkene was extended to 4 and 5 carbons. Butene oxime sugar **177** and pentene oxime sugar **178** (Scheme 5-19) were synthesised following the same procedure as for the propene oxime sugar. However, only the synthesis of the butene analogue will be discussed with the yields of the pentene analogue shown in parenthesis.

N-butenyloxyphthalimide **179** was synthesised following Mitsunobu reaction from hydroxyphthalimide **164** by addition of diethyl azodicarboxylate to the reaction mixture. After buten-1-ol was added, the reaction mixture was stirred for 24 hours and purification using flash chromatography afforded *N*-butenyloxyphthalimide **179** in 77 % yield (**180**, 89 %, Scheme 5-18).



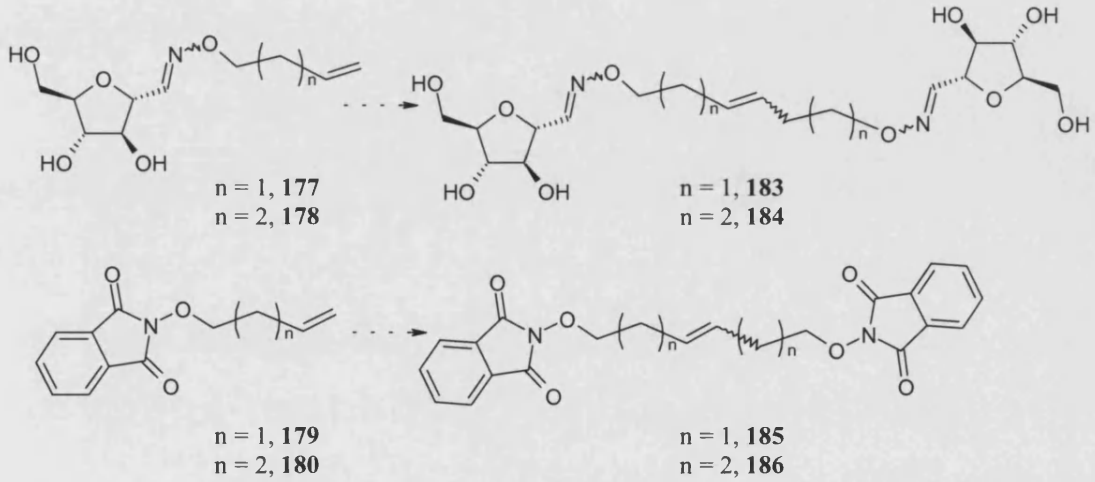
Scheme 5-18: Synthesis of *N*-butenyloxyphthalimide **179**: i- buten-1-ol, diethyl azodicarboxylate, triphenylphosphine, tetrahydrofuran, 24 h, r.t., 77 % (89 %).

The phthalimide protecting group was cleaved by heating intermediate **179** at reflux in the presence of hydrazine hydrate in ethanol for two hours, with the subsequent work-up producing the hydrochloride salt **181** in 77 % yield (**182**, 77 %, Scheme 5-19) . This was then added to 2,5-anhydro-*D*-mannose **152** in the presence of pyridine and the desired oxime **177** was afforded after purification in 36 % yield (**178**, 39 %).



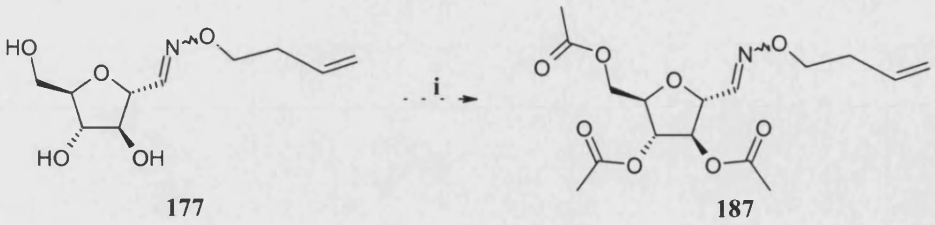
Scheme 5-19: Synthesis of oxime sugars **177** and **178**: **i**- hydrazine hydrate, ethanol, reflux, 2 h, 77 % (77 %); **ii**- pyridine, dimethylformamide, r.t., 20 h, 36 % (39 %).

These new substrates were subjected to olefin-cross metathesis using second generation Grubbs catalyst **7** and did not produce the desired products. Precursors **179** and **180** were also tested (Scheme 5-20) with no observed reaction.



Scheme 5-20: Attempt of olefin metathesis of butenoxime and pentenoxime sugars **177** and **178** and their precursor.

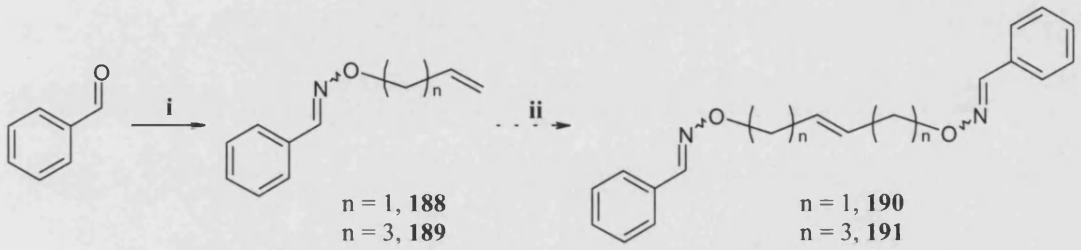
Following the unsuccessful production of the chain-lengthened cross-metathesis products **183-186**, the protected butenoxime sugar **187** was also synthesised (Scheme 5-21) and tested in olefin-cross metathesis in dichloromethane, again, no conversion was observed.



177 187

Scheme 5-21: Synthesis of protected butenoxime **187**: **i**- acetic anhydride, pyridine, r.t., 16 h, 72 %.

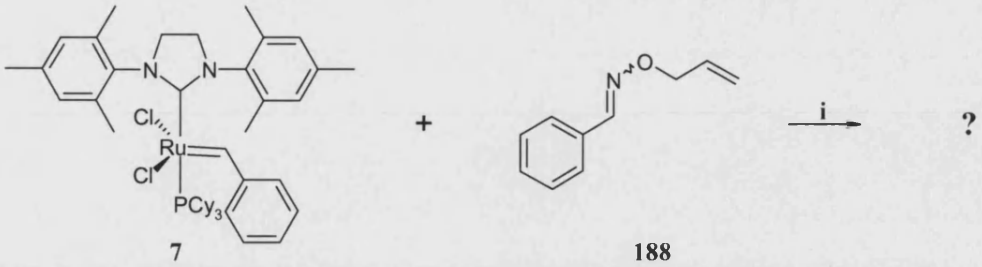
In order to discover if the inhibition was caused, by the hydroxyl groups of the sugar complexing with the ruthenium, oximes with no hydroxyl groups were synthesised (**188** in 89 % and **189** in 86 % yield) using the same method used for the synthesis of oxime sugars (Scheme 5-22).



Scheme 5-22: Synthesis of oxime substrates **188** and **189** and subsequent attempted olefin cross metathesis: **i**- **166** (**182**), pyridine, dimethylformamide, r.t., 20 h, 89 % (86 %); **ii**- **7**, $CDCl_3$, 90 min, 45 °C.

These compounds were subjected to olefin-cross metathesis which did not produce products **190** and **191**, however, it was noticed that not all of the starting material was recovered.

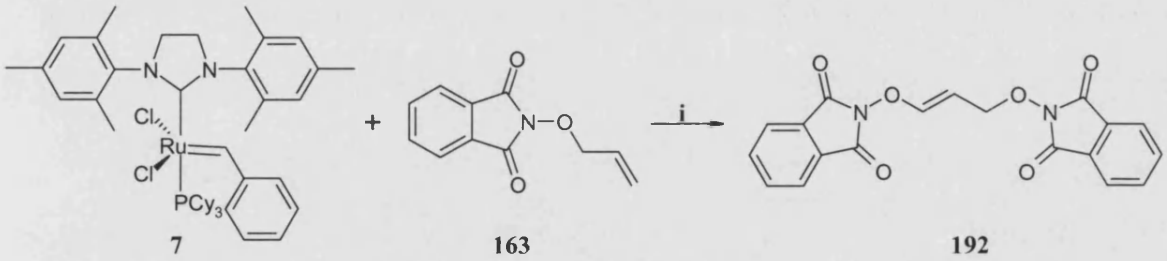
A stoichiometric reaction was performed between Grubbs second generation catalyst **7** and benzyloxime **188** in order to determine whether the ruthenium complex was reacting with the substrate to form an inactive product (Scheme 5-23). The reaction was stirred for 2 hours at 45 °C and the resulting mixture was subjected to TLC which showed a mixture of the catalyst, the starting material and an unknown product.



7 188

Scheme 5-23: Attempted synthesis of ruthenium complex: **i**- $CDCl_3$, 2 h, 45 °C.

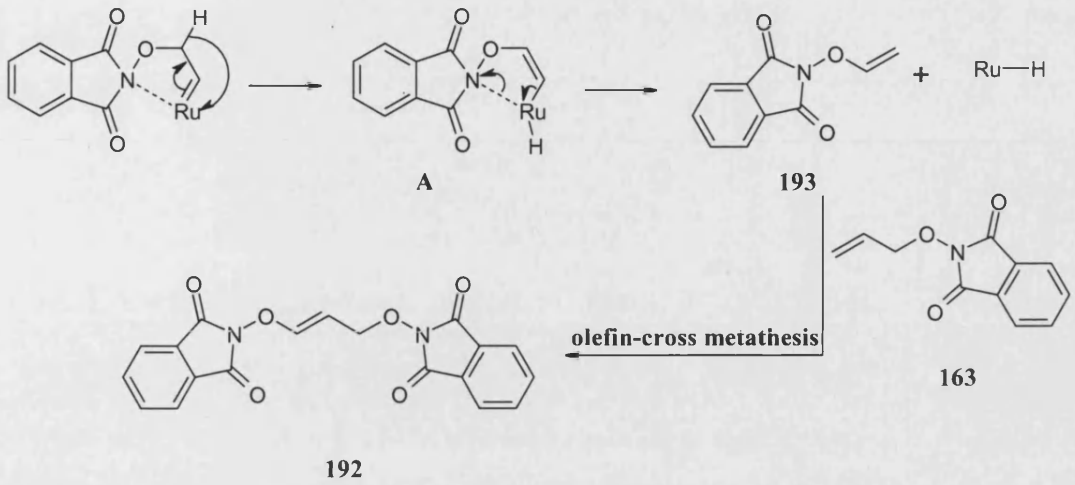
Unfortunately, the ^1H NMR spectra of the unknown compound gave no information about the structure of the complex. It was therefore decided to try this reaction with allyloxyphthalimide which showed no conversion in olefin cross metathesis, possibly for the same reasons. After separation of the different fractions using column chromatography, ^1H NMR showed the presence of phosphine, starting material and a new compound, which was identified to be compound **192** (Scheme 5-24).



7 163 192

Scheme 5-24: Stoichiometric reaction between second generation Grubbs catalyst **7** with allyloxyphthalimide: **i**- $CDCl_3$, 2 h, 45 °C, 25 %.

The study of second generation Grubbs ruthenium catalyst, when used with substrates requiring high temperature and long reaction times, showed an occurrence of both olefin metathesis and olefin isomerisation.[35] In our case, it seems that part of the initiator isomerises a portion of the substrate to compound **193** (Scheme 5-25), which was then subjected to olefin-cross metathesis. It is also possible that some of the ruthenium is transformed to a hydride ruthenium complex which has no olefin metathesis activity.



Scheme 5-25: Possible mechanism for the isomerisation of allyloxyphthalimide and subsequent olefin-cross metathesis.

Formation of this hydride complex may have been responsible for the inhibition of olefin metathesis when catalytic quantities were used under these conditions. Isomerisation products could not be identified due to the small amounts present. The fact that olefin metathesis of allylphthalimide **174** occurs maybe because the formation a four membered ring equivalent to **A** (Scheme 5-25) is improbable due to ring strain.

5.3 Summary

Our interest was to synthesise allyl substituted sugars that could be used in olefin-cross metathesis in order to provide a small library of potential fructose transport inhibitors. Unfortunately, none of the synthetic sugars were effectively converted when subjected to olefin-cross metathesis using the highly efficient second generation Grubbs catalyst. The subsequent investigation showed that the solubility was not responsible for such poor results. The length of the chain supporting the alkene moiety was increased because it was thought that the ruthenium active species was complexing with the aminoxy group, therefore inhibiting any possible olefin metathesis reaction. As the structural changes did not affect the results, a stoichiometric reaction using precursor **163** with second generation catalyst **7** was performed to explore whether a different reaction inhibits the expected olefin-cross metathesis. This reaction produced an isomeric compound and possibly a hydride ruthenium complex, which, for the allyl derivatives at least, demonstrated that the aminoxy moiety is responsible for the complexation of the ruthenium and inhibition of catalysis. This explains the inefficiency

of olefin-cross metathesis of the alkene oxime substrates, but we have been unable to explain why the allylamino sugar does not react.

6.0 Conclusion

Our group has previously developed the synthesis of vinyl-supported pre-catalyst **41**, which proved to be problematic due to polymerization of 2-vinylphenol in the first two steps of the synthesis. Using commercially available propenyl phenol, which does not polymerize, we hoped to improve the overall yield of the synthesis, keeping the same reactivity of the initiator. This new pre-catalyst was tested for ring-closing metathesis but unfortunately, its reactivity and recyclability were not comparable to vinyl-supported initiator **41**. It was then decided to synthesise the vinyl ligand responsible for high reactivity by introducing the vinyl moiety at a later stage in the synthesis by performing a Wittig reaction on an aldehyde. This aldehyde was first subjected to alkylation with methyl 5-bromohexanoate **42**, then converted under Wittig conditions, forming the vinyl intermediate which was hydrolysed and attached to polymer support. Comparison of the newly synthesised vinyl-supported initiator with the propenyl analogue confirmed the superiority of the vinyl pre-catalyst **41**. We conclude from these experiments that in order to maintain the reactivity of the initiator, excess ligand has to rapidly recapture the active ruthenium methylidene species *via* olefin metathesis, otherwise it decomposes. This reaction is faster with the vinyl ligand than with propenyl, thus explaining the loss in reactivity and consequent poor recyclability of the propenyl-supported pre-catalyst.

Second generation vinyl-polystyrene-supported initiator **88** was synthesised and tested in ring-closing metathesis and cross metathesis, showing a higher efficiency as well as a better recyclability compared to the first generation analogue **41**. As expected, the differing electronic properties obtained by exchanging the phosphine ligand with an imidazolylidene carbene afforded a more stable and active complex.[32] In order to explore the reactivity of the second generation initiator in water, it was attached to a hydrophilic resin (amino PEGA) allowing catalytic activity in polar solvents, especially in the cross metathesis of allyl alcohol in water at 45 °C (85 %). It was then decided to try to enhance its efficiency by substituting the phenyl moiety of the ligand with nitro and methoxy functionalities which accelerate the dissociation of the *O*-^{i}Pr moiety during initiation of olefin metathesis. A study comparing nitro, methoxy and non-substituted second generation PEGA **104** supported initiators showed comparable reactivity between the methoxy and **104**. However, its recyclability decreased regularly after each use. The nitro-analogue showed lower activity than the two other initiators and a practically non-existent recyclability. This may be due to poor efficiency in the loading

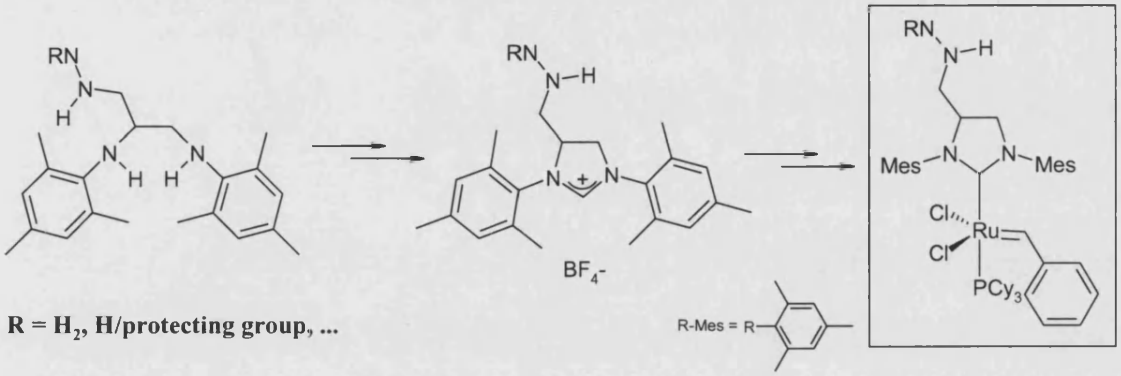
of Grubbs second generation catalyst during the synthesis of the initiator or problems in recapturing the ruthenium methylidene **27**.

One of our aims was to synthesise inhibitors in the presence of a biological target *via* olefin metathesis, therefore the development of a catalyst efficient in water was of interest. By modifying the imidazolylidene ligand responsible for the high efficiency of the second generation catalyst, we hoped to change the solubility and aqueous stability of the new pre-catalyst. Several synthetic pathways involving a glyoxal moiety were unsuccessful, therefore, precursor *N,N'*-dimesityl-2,3-diamino-1-propanol **136** was synthesised and substituted with *N*-hydroxyphthalamide. The imidazole ring was closed following Arduengo's method, but could not be attached to Grubbs first generation catalyst, probably due to poor solubility in various solvents (hexane, tetrahydrofuran and toluene).

Finally, allyl-substituted sugars were synthesised to be used in olefin-cross metathesis for the production of a small library of potential fructose transport inhibitors (GLUT5 inhibitors). Unfortunately, the reaction did not produce the expected compounds, with subsequent investigations showing that the poor solubility of the sugar substrates was not responsible for such poor results. Different modifications were performed in order to eliminate a possible complex formation between the ruthenium active species and the oxyamino group supporting the alkene moiety that may inhibit olefin metathesis, but these alterations did not improve yields. A stoichiometric reaction using allyloxyphthalimide **163** was performed in order to identify any products that may inhibit olefin metathesis. Isolation of an isomeric compound suggested the possible role for a hydride ruthenium complex, perhaps a result of ruthenium complexation by the oxy-amine moiety. It was established that the alkene moiety cannot be linked to the sugar *via* an oxime, due to its inefficiency in olefin-cross metathesis, but we have been unable to explain why the allylamino sugar does not react.

Water-soluble imidazolylidene supported catalysts

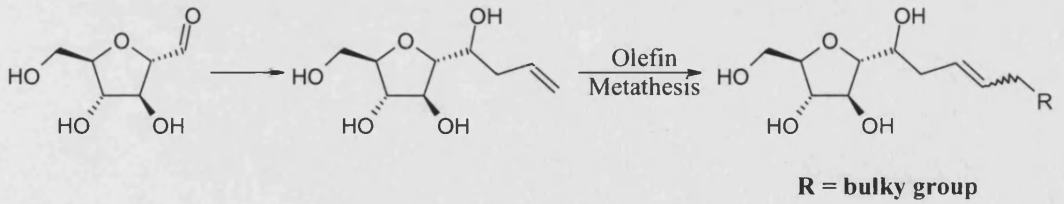
The problem of solubility of our newly synthesised imidazolylidene ligand was not resolved and further investigation was not possible due to lack of time. It would have been interesting to link other types of substituents to the imidazolylidene moiety, such as hydrazines in order to vary this solubility (Scheme 6-1). The use of a variety of protecting groups could have improved the understanding of the solubility of such ligands.



Scheme 6-1: Possible pathway towards polar-solvent-soluble catalysts.

Synthesis of fructose analogues towards GLUT5 inhibitors

The study of oxime sugars proved that this type of functional group cannot be used in olefin metathesis due to its complexation with the ruthenium active species. Therefore, the introduction of the allylic moiety onto the sugar by different means could be investigated (Scheme 6-2). This would allow the synthesis of a wide range of substrates that could be used in olefin metathesis, creating possible inhibitors that could help the understanding of glucose transporter GLUT5.



Scheme 6-2: Possible target that could be used in olefin metathesis, towards a library of GLUT5 inhibitors.

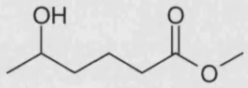
7.0 Experimental

General methods

All chemicals were purchased from Acros, Aldrich, Lancaster or Fluka. Tetrahydrofuran was obtained by distillation from sodium/benzophenone ketyl. All other reagents were used as supplied unless otherwise stated. Thin Layer Chromatography was performed with silica gel 60 pre-coated aluminium plates (0.20 mm thickness) from Macherey-Nagel, with visualisation by UV light (254 nm) and stains (potassium permanganate, anisaldehyde in ethanol and phosphomolybdic acid in methanol). Flash chromatography was performed on silica gel Matrex 60 from Fisher Chemicals. Infrared spectra were determined as KBr discs or films as stated using Perkin-Elmer Spectrum RXI FT-IR and peak positions are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with either a JEOL JMN GX-270 or EX-400 spectrometers, the chemical shifts are reported in parts per million (ppm) and *J* values are quoted in Hz. Mass spectra were recorded at the University of Bath mass spectrometry service using a VG Autospec. FAB mass spectra were carried out using 3-nitrobenzyl alcohol (NOBA) as the matrix. Degassing of solvents was achieved by three cycles of freeze-pump-thaw. Ruthenium elemental ICP-AES analyses of polymer-supported initiators were performed by MEDAC LTD., Surrey, UK. Melting points were determined using a Reichert-Jung Therm Galen Kofler block.

7.1 Improvement of polymer-supported initiator's synthesis

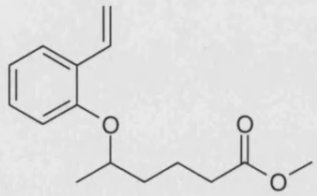
Methyl 5-hydroxyhexanoate 42[92]



A mixture of fresh sodium (0.20 g, 8.8 mmol) in methanol (15 mL) was added *via* a cannula to δ-hexanolactone **48** (1.0 g, 8.8 mmol) in dry methanol (30 mL). The reaction mixture was stirred for 4 hours, acetic acid (0.63 g, 10 mmol) was added and the reaction mixture stirred for 15 minutes then concentrated under reduced pressure. To the mixture was added dichloromethane (100 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL). The aqueous layers were then back extracted with dichloromethane (3 x 50 mL) and the combined organics were dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the ester **42** (1.2 g, 94 %) as a colourless oil. R_f 0.36 (1:4 ethyl acetate:hexane); ν_{max} cm^{-1} (film) 3419 (O-H), 3000-2850 (C-H), 1732 (C=O), 1439 (-CH), 1374 (CH_3), 1170 (C-O), 1131 (-

OH); δ_H (400 MHz; $CDCl_3$) 3.71 (1H, sextet, *J* = 6.0 Hz, C*H*CH_3), 3.59 (3H, s, CH_3O), 2.36 (1H, s, O*H*), 2.26 (2H, t, *J* = 7.3 Hz, CH_2CO), 1.71-1.54 (2H, m, CH_2CH), 1.42-1.35 (2H, m, CH_2), 1.11 (3H, d, *J* = 6.0 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 174.3 (C), 67.6 (CH), 51.9 (CH_3), 38.9 (CH_2), 34.2 (CH_2), 23.8 (CH_3), 21.5 (CH_2); m/z [FAB^+] 147.1 (M^++H, 86 %).

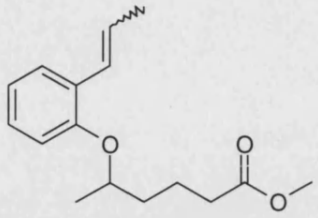
Methyl 5-(2-vinylphenoxy)hexanoate 45[128]



2'-Hydroxycinnamic acid (1.5 g, 9.1 mmol) was heated at 210 °C under vacuum (≤ 1 mmHg) in a Kugelröhr apparatus, previously lined with freshly sublimed 1,4-benzoquinone. 2-Vinylphenol was collected in a flask externally cooled using dry ice and acetone. The resulting oil containing 2-vinylphenol with benzoquinone was used without further purification. Di-*iso*-propyl azodicarboxylate (3.0 mL, 14mmol) in anhydrous tetrahydrofuran (15 mL) was added to a stirring solution of the above crude methyl 5-hydroxyhexanoate **42** (2.0 g, 14 mmol) and triphenylphosphine (5.0 g, 19 mmol) in anhydrous tetrahydrofuran (30 mL) at 0 °C. After 17 hours, the reaction mixture was concentrated and then purified by flash chromatography using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent to afford compound **45** as a colourless oil (0.17 g, 8 %). R_f 0.35 (15:85 diethyl ether: hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1738 (C=O), 1643 (C=C), 1482 (C=C), 1453 (-CH), 1379 (CH_3), 1239 (C-O), 1171 (C-O-C); δ_H (400 MHz; $CDCl_3$) 7.51-6.86 (5H, m, Ar*H* and C*H*=CH_2), 5.73 (1H, dd, *J* = 18.0, 1.6 Hz, C$H_{(trans)}$=CH), 5.24 (1H, dd, *J* = 11.3, 1.6 Hz, C$H_{(cis)}$=CH), 4.41 (1H, sextet, *J* = 6.0 Hz, C*H*CH_3), 3.67 (3H, s, CH_3O), 2.37 (2H, t, *J* = 7.0 Hz, CH_2CO), 1.87-1.62 (4H, m, CHCH_2CH_2), 1.32 (3H, d, *J* = 6.0 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 174.0 (C), 155.2 (C), 132.0 (ArCH), 128.9 (ArCH), 128.0 (C), 126.7 (ArCH), 120.8 (ArCH), 114.2 (=CH_2), 113.9 (=CH), 74.3 (CHO), 51.9 (CH_3), 36.3 (CH_2), 34.3 (CH_2), 21.5 (CH_2), 20.2 (CH_3); m/z [FAB^+] 249.2 (M^++H, 12%).

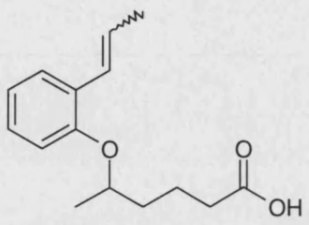
7.1.1 Propenyl route

Methyl 5-(2-(prop-1-enyl)phenoxy)hexanoate 550



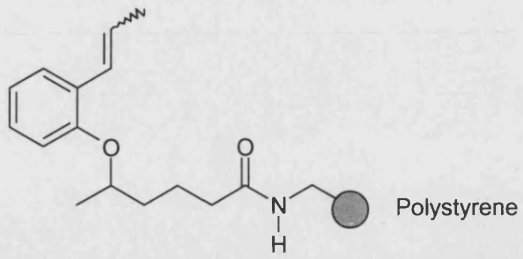
Di-*iso*-propyl azodicarboxylate (0.25 mL, 1.2 mmol) in anhydrous tetrahydrofuran (0.75 mL) was added dropwise to a solution of methyl 5-hydroxyhexanoate **42** (0.17 g, 1.2 mmol), 2-(prop-1-enyl)phenol (0.10 mL, 0.77 mmol) and triphenylphosphine (0.42 g, 1.6 mmol) in anhydrous tetrahydrofuran (1.50 mL) at 0 °C . The reaction mixture was stirred for 24 hours under nitrogen at room temperature then concentrated under reduced pressure to leave a yellow oil, which was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 4:96) as eluent to give the ether **50** (0.17 g, 83 %, 3:1 *E*:*Z*) as a colourless oil. R_f 0.39 (1:4 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1739 (C=O), 1597 (C=C), 1450 (-CH), 1374 (CH_3), 1239 (C-O), 1135 (C-O-C); δ_H (400 MHz; $CDCl_3$) 7.41 (0.8H, dd, J = 7.8 1.6 Hz, Ar$H_{(trans)}$), 7.28 (0.2H, dd, J = 7.8, 1.6 Hz, Ar$H_{(cis)}$), 7.21-6.83 (3H, m, Ar*H*), 6.72 (0.8H, dd, J = 16.0, 1.6 Hz, C*H*=C$H_{(trans)}CH_3$), 6.55 (0.2H, dd, J = 11.7, 1.6 Hz, C*H*=C$H_{(cis)}CH_3$), 6.21 (0.8H, dq, J = 16.0, 6.8 Hz, CH=C$H_{(trans)}CH_3$), 5.79 (0.2H, dq, J = 11.7, 6.8 Hz, CH=C$H_{(cis)}CH_3$), 4.37 (1H, sextet, J = 5.9 Hz, C*H*CH_3), 3.66 (3H, s, CH_3O), 2.35 (2H, t, J = 7.1 Hz, CH_2CO), 1.90 (3H, dd, J = 6.8, 1.6 Hz, CH_3CH=), 1.86-1.61 (4H, m, CH_2CH_2), 1.31 (3H, d, J = 5.9 Hz, CHCH_3); δ_C (100 MHz; $CDCl_3$) 173.7 (C), 154.3 (C), 130.1 (=CH), 127.4 (=CH), 126.2 (ArCH), 126.1 (C), 125.7 (ArCH), 120.5 (ArCH), 113.7 (ArCH), 73.9 (CHO), 51.5 (CH_3), 35.9 (CH_2), 34.0 (CH_2), 21.1 (CH_2), 19.8 (CH_3), 19.0 (CH_3); m/z [FAB$^+$] 262.2 (M^++H, 28 %) [found 262.1580 $C_{16}H_{22}O_3$ expected 262.1569].

5-(2-(Prop-1-enyl)phenoxy)hexanoic acid 51



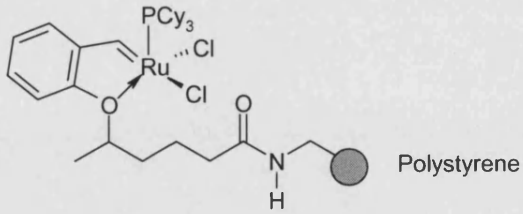
Sodium hydroxide (1 M, 4.5 mL, 4.5 mmol) was added to a solution of methyl 5-(2-(prop-1-enyl)phenoxy)hexanoate **50** (0.88 g, 3.3 mmol) in 1,4-dioxane (8 mL) at room temperature and the reaction mixture was stirred for 7 hours, and concentrated under vacuum. Diethyl ether (30 mL) and water (30 mL) were added to the resulting oil and the aqueous phase was washed with diethyl ether (3 x 30 mL). The combined organic phases were extracted with water (3 x 30 mL). The combined aqueous phases were acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 40 mL). The combined organics were washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the acid **51** (0.75 g, 90 %, 3:1 *E*:*Z*) as a yellow oil. R_f 0.04 (15:85 ethyl acetate: hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 2800-2500 (O-H), 1708 (C=O), 1596 (C=C), 1449 (-CH), 1377 (CH_3), 1239 (C-O), 1135 (C-O-C); δ_H (400 MHz; $CDCl_3$) 7.41 (0.8H, dd, J = 7.6, 1.6 Hz, Ar$H_{(trans)}$), 7.28 (0.2H, dd, J = 7.6, 1.6 Hz, Ar$H_{(cis)}$), 7.21-6.83 (3H, m, Ar*H*), 6.71 (0.8H, dd, J = 16.0, 1.6 Hz, C*H*=C$H_{(trans)}CH_3$), 6.54 (0.2H, dd, J = 11.7, 1.6 Hz, C*H*=C$H_{(cis)}CH_3$), 6.20 (0.8H, dq, J = 16.0, 6.8 Hz, CH=C$H_{(trans)}CH_3$), 5.79 (0.2H, dq, J = 11.7, 1.6 Hz, CH=C$H_{(cis)}CH_3$), 4.41-4.35 (1H, sextet, J = 6.0 Hz, C*H*CH_3), 2.43-2.38 (2H, m, CH_2CO), 1.89 (3H, dd, J = 6.8, 1.6 Hz, CH_3CH=), 1.86-1.64 (4H, m, CH_2CH_2), 1.31 (3H, d, J = 6.0 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 179.5 (C), 154.6 (C), 128.4 (ArCH), 127.8 (C), 126.6 (ArCH), 126.2 (CH=), 125.9 (ArCH), 120.9 (ArCH), 114.0 (CH=), 74.3 (CHO), 36.2 (CH_2), 34.2 (CH_2), 21.2 (CH_2), 20.2 (CH_3), 19.4 (CH_3); m/z [FAB^+] 248.2 (M^+, 59 %) [found 248.1418 $C_{15}H_{20}O_3$ expected 248.1412].

5-(2-(Prop-1-enyl)phenoxy)hexanoylamino-polystyrene 52



Di-*iso*-propylcarbodiimide (0.45 mL, 2.8 mmol) and 1-hydroxybenzotriazole (0.39 g, 2.8 mmol) were added to 5-(2-(prop-1-enyl)phenoxy)hexanoic acid **51** (0.71 g, 2.8 mmol) in dichloromethane:dimethylformamide (1:1, 2 mL). The reaction mixture was stirred for 10 minutes and then added to the resin (amino methyl resin SS, loading approx. 1.1-1.6 $mmol.g^{-1}$) (0.22 g, 0.29 mmol) in dichloromethane: dimethylformamide (1 mL, 1:1). The reaction mixture was stirred for 15 hours by vertical rotation, on a blood rotator. Remaining acid was recovered by washing the resin with dichloromethane. The resin was washed with sequential portions of dichloromethane, tetrahydrofuran, dimethylformamide, dimethylformamide:methanol (1:1), dimethyl-formamide, tetrahydrofuran and dichloromethane. The resin was then dried under reduced pressure to obtain the resin **52** (0.29 g). (A small portion of the resin was subjected to Kaiser test, which was negative). ν_{max} cm^{-1} (film) 1668 ($C{=}O_{amide}$).

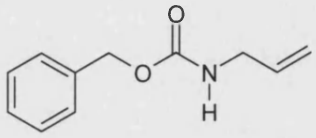
Aminopolystyrene-supported ruthenium initiator 53



A sonicated solution of Grubbs catalyst (24 mg, 29 μmol) in degassed 1,2-dichloroethane (1 mL) was added to a suspension of 5-(2-propenylphenoxy)hexanoylamino-polystyrene **52** (0.29 g, 0.29 mmol) in 1,2-dichloroethane (1 mL). The reaction mixture was agitated by vertical rotation for two hours at room temperature. The resin was then washed with dichloromethane until the filtrate was clear. This entire operation was repeated five times and the resin **53** was finally dried in a drying pistol to afford the polystyrene-supported initiator as brown beads.

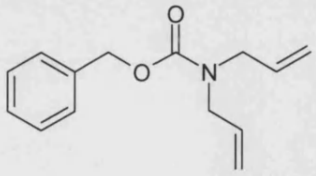
7.1.2 Synthesis of olefin metathesis acyclic diene substrates

Benzyl *N*-(prop-2-enyl)carbamate 57[129]



Benzyl chloroformate **56** (2.5 mL, 17 mmol) was added dropwise to a solution of allylamine (1.6 mL, 21 mmol) in dichloromethane (10 mL) and the reaction mixture was stirred at 0 °C for 4 hours then concentrated under vacuum. The residue was partitioned between diethyl ether (25 mL) and water (25 mL) and the aqueous phase was acidified by addition of hydrochloric acid (1 M) and then extracted with diethyl ether (4 x 30 mL). The combined organic phases were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to leave a yellow oil. Purified by flash chromatography on silica using a gradient of ethyl acetate:hexane (0:100 → 5:95) as eluent gave compound **57** (2.2 g, 67 %). R_f 0.23 (1:4 ethyl acetate:hexane); ν_{max} cm^{-1} (film) 3425 (N-H), 3100-3000 (ArH), 3000-2850 (C-H), 1698 (C=O), 1646 (C=C), 1522 (C=C), 1455 (-CH), 1249 (C-O); δ_H (400 MHz; $CDCl_3$) 7.56-7.29 (5H, m, Ar*H*), 5.85 (1H, m, C*H*=CH_2), 5.19 (1H, ddt, *J* = 17.2, 1.6, 1.6 Hz, CH=C$H_{(trans)}$), 5.14 (1H, ddt, *J* = 10.1, 1.6, 1.6 Hz, CH=C$H_{(cis)}$), 5.12 (2H, s, CH_2O), 4.83 (1H, bs, N*H*), 3.83 (2H, t, *J* = 5.5 Hz, CH_2NH); δ_C (100 MHz; $CDCl_3$) 156.5 (C), 136.3 (C), 134.3 (=CH), 128.4 (2xArCH), 128.3 (ArCH), 128.0 (2xArCH), 116.3 (=CH_2), 66.8 (CH_2), 43.5 (CH_2).

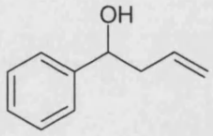
Benzyl *N*,*N*-di(prop-2-enyl)carbamate 54[130]



Benzyl *N*-(prop-2-enyl)carbamate **57** (1.0 g, 5.2 mmol) was added to a suspension of sodium hydride (0.25 g, 6.2 mmol) in anhydrous dimethylformamide (20 mL) and the reaction mixture was stirred at room temperature for 15 minutes after which allyl bromide (0.55 mL, 6.3 mmol) was added. After 20 hours, the reaction mixture was quenched with ice and saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with diethyl ether (4 x 40 mL) and the combined organics were washed with

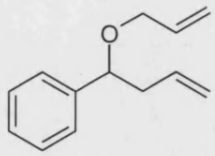
brine (60 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The Kugelröhr distillation provided benzyl *N*,*N*-di(prop-2-enyl)carbamate **54** as colourless oil (0.63 g, 26 %). R_f 0.44 (15:85 ethyl acetate:hexane); ν_{max} cm^{-1} (film) 3436 (N-H), 3100-3000 (ArH), 3000-2850 (C-H), 1702 (C=O), 1646 (C=C), 1498 (C=C), 1459 (-CH), 1240 (C-O); δ_H (400 MHz; $CDCl_3$) 7.49-7.19 (5H, m, Ar*H*), 5.71-5.67 (2H, m, C*H*=CH_2), 5.15-5.01 (6H, m, CH=CH_2, CH_2O), 3.81 (4H, b, CH_2N); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 137.0 (C), 133.7 (2 x =CH), 128.6 (2 x ArCH), 128.1 (ArCH), 128.0 (2 x ArCH), 117.4 (=CH_2), 116.9 (=CH_2), 67.5 (CH_2), 49.5 (CH_2), 48.9 (CH_2); m/z [FAB^+] 232.2 (M^++H, 7 %) [found 232.1332 $C_{14}H_{18}NO_2$ expected 232.1338].

1-Phenylbut-3-en-1-ol 60[131]



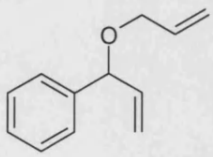
Tetrahydrofuran (15 mL) and water (5 mL) were added to a mixture of aluminium powder (0.53 g, 19 mmol) and bismuth chloride (6.1 g, 19 mmol) (Caution: exothermic). Benzaldehyde **59** (1.0 mL, 9.8 mmol) and allyl bromide (1.7 mL, 20 mmol) were added and the reaction mixture was stirred at room temperature for 17 hours, then quenched with a saturated aqueous ammonium chloride solution. The reaction mixture was then filtered through Celite and the organic materials extracted with diethyl ether (3 x 20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 10:90) as eluent gave compound **60** (1.3 g, 89 %). R_f 0.36 (1:2 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3350 (OH), 3100-3000 (=CH), 3000-2850 (C-H), 1641 (C=C), 1493 (C=C), 1449 (C=C), 1046 (C-O); δ_H (400 MHz; $CDCl_3$) 7.42-7.26 (5H, m, Ar*H*), 5.82 (1H, ddt, *J* = 17.2, 10.1, 7.4 Hz, C*H*=CH_2), 5.20-5.13 (2H, m, CH_2=CH), 4.74 (1H, t, *J* = 6.2 Hz, C*H*OH), 2.58-2.46 (2H, m, CH_2), 2.17 (1H, s, O*H*); δ_C (100 MHz; $CDCl_3$) 144.0 (C), 134.7 (=CH), 128.6 (2 x ArCH), 127.8 (ArCH), 126.0 (2 x ArCH), 118.7 (=CH_2), 73.6 (CH), 44.3 (CH_2).

(1-(Prop-2-enyloxy)but-3-enyl)benzene 58[94]



1-Phenylbut-3-en-1-ol **60** (1.3 g, 8.6 mmol) in dry tetrahydrofuran (20 mL) was added dropwise over 15 minutes, at 0 °C, to sodium hydride (0.86 g, 21 mmol) in dry tetrahydrofuran (20 mL). After 15 minutes, allyl bromide (2.1 mL, 17 mmol) was added dropwise and the reaction mixture was stirred for 16 hours at room temperature. The mixture was then acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 30 mL). The organic layer was washed with brine (30 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford (1-(prop-2-enyloxy)but-3-enyl)benzene **58** (1.4 g, 87 %). R_f 0.82 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (=CH), 3000-2850 (C-H), 1642 (C=C), 1453 (C=C), 1087 (C-O); δ_H (400 MHz; $CDCl_3$) 7.38-7.26 (5H, m, Ar*H*), 5.96-5.86 (1H, m, OCH_2CH=), 5.80 (1H, ddt, *J* = 17.1, 10.1, 7.2 Hz, $CHCH_2CH$=), 5.25 (1H, dq, *J* = 17.1, 1.6 Hz, OCH_2CH=$CH_{(trans)}$), 5.19 (1H, dq, *J* = 10.1, 1.6 Hz, OCH_2CH=$CH_{(cis)}$), 5.09-5.01 (2H, m, CH=CH_2), 4.35 (1H, t, *J* = 6.1 Hz, C*H*O), 3.94 (1H, ddt, *J* = 12.7, 5.3, 1.6 Hz, CH_aH_bO), 3.78 (1H, ddt *J* = 12.7, 6.1, 1.2 Hz, CH_aH_bO), 2.62 (1H, ddd, *J* = 12.7, 7.2, 1.2 Hz, $CHCH_aH_bCH$=), 2.44 (1H, ddd, *J* = 12.7, 7.2, 1.2 Hz, $CHCH_aH_bCH$=); δ_C (100 MHz; $CDCl_3$) 142.1 (C), 135.1 (=CH), 135.0 (=CH), 128.5 (2 x ArCH), 127.8 (ArCH), 127.0 (2 x ArCH), 117.1 (=CH_2), 117.0 (=CH_2), 81.5 (CH), 69.8 (CH_2), 43.0 (CH_2); m/z [CI^+] 189.0 (M^++H, 30 %).

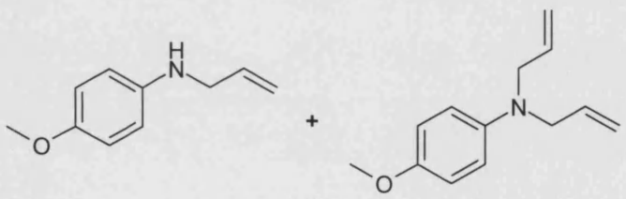
(1-(Prop-2-enyloxy)prop-2-enyl)benzene 62[132;96]



1-Phenylprop-2-en-1-ol **63** (0.10 mL, 0.76 mmol) in dry tetrahydrofuran (3 mL) was added dropwise, to sodium hydride (76 mg, 1.9 mmol) in dry tetrahydrofuran (3 mL) at 0 °C. After 15 minutes, allyl bromide (0.10 mL, 1.5 mmol) was added dropwise and the reaction mixture was stirred for 16 hours at room temperature. The mixture was then

acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The product was finally distilled with the Kugelröhr to afford compound **62** as a colourless oil (82 mg, 62 %). R_f 0.52 (15:85 diethyl ether: hexane); ν_{max} cm^{-1} (film) 3100-3000 (=CH), 3000-2850 (C-H), 1641 (C=C), 1490 (C=C), 1450 (-CH), 1415 (CH_3), 1070 (C-O); δ_H (400 MHz; $CDCl_3$) 7.39-7.26 (5H, m, Ar*H*), 6.02-5.91 (2H, m, 2 x C*H*=CH_2), 5.33-5.27 (2H, m, CH_2CH=CH_2), 5.21 (1H, dd, *J* = 8.8, 1.6 Hz, CHCH=C$H_{(trans)}$), 5.21 (1H, dd, *J* = 8.8, 1.6 Hz, CHCH=C$H_{(cis)}$), 4.82 (1H, d, *J* = 6.6 Hz, C*H*O), 4.05 (1H, ddt, *J* = 12.7, 5.5, 1.6 Hz, OC$H_a$$H_b$), 3.96 (1H, ddt, *J* = 12.7, 5.5, 1.6 Hz, OC$H_a$$H_b$); δ_C (100 MHz; $CDCl_3$) 140.8 (C), 138.7(=CH), 134.6 (=CH), 128.3 (2 x ArCH), 127.5 (ArCH), 126.7 (2 x ArCH), 116.7 (=CH_2), 116.2 (=CH_2), 82.0 (CH), 69.2 (CH_2); m/z [CI^+] 174.0 (M^++H, 14 %).

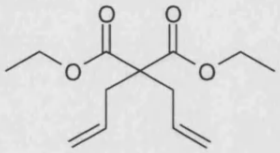
_N_-(Prop-2-enyl)-4-methoxyphenylamine 66[133], _N,N_-di(prop-2-enyl)-4-methoxyphenylamine 64[133;134]



4-Methoxyaniline **65** (3.0 g, 24 mmol) in dry tetrahydrofuran (20 mL) was added to a solution of sodium hydride (2.4 g, 53 mmol) in dry tetrahydrofuran (40 mL) at 0 °C. The mixture was stirred for 15 minutes, then allyl bromide (3.5 g, 29 mmol) was added dropwise and the solution was stirred for 20 hours. The reaction mixture was quenched with ice, acidified with hydrochloric acid (1 M) and partitioned between diethyl ether (50 mL) and water (50 mL). The aqueous phase was washed with diethyl ether (3 x 30 mL) and the combined organics washed with brine (3 x 30 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give the compounds *N*-(prop-2-enyl)-4-methoxyphenylamine **66** (1.8 g, 46 %) and *N,N*-(diprop-2-enyl)-4-methoxyphenylamine **64** (0.72 g, 15 %) which were isolated as oils using flash chromatography on silica gel. **66**: R_f 0.33 (15:85 diethyl ether: hexane); ν_{max} cm^{-1} (film) 3391 (N-H), 3100-3000 (=CH), 3000-2850 (C-H), 1619 (C=C), 1643 (C=C), 1513 (C=C), 1463 (-CH), 1233 (CH_3-O-Ar), 995 (CH=CH_2), 819 (C-H); δ_H (400 MHz; $CDCl_3$) 6.83-6.60 (4H, m, Ar*H*), 5.98 (1H, ddt, *J* = 17.2, 11.0, 5.5 Hz, C*H*=CH_2), 5.32-5.15 (2H,

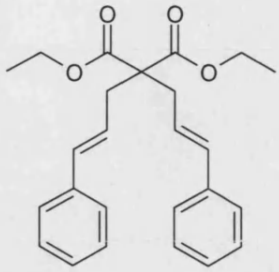
m, CH_2=CH), 3.76 (3H, s, CH_3), 3.74 (2H, m, CH_2NH), 3.54 (1H, bs, N*H*); δ_C (100 MHz; $CDCl_3$) 152.4 (C), 142.5 (C), 136.0 (=CH), 116.2 (=CH_2), 115.2 (2 x ArCH), 114.6 (2 x ArCH), 56.2 (CH_3), 48.0 (CH_2); m/z [FAB$^+$] 163.1 (M^+, 100 %). **64**: R_f 0.53 (15:85 diethyl ether: hexane); ν_{max} cm^{-1} (film) 3100-3000 (=CH), 3000-2850 (C-H), 1641 (C=C), 1577 (C=C), 1512 (C=C), 1465 (-CH), 1441 (-CH), 1384 (-CH_3), 1241 (CH_2-O-Ar), 991 (CH=CH_2), 918 (CH=CH_2), 813 (C-H); δ_H (400 MHz; $CDCl_3$) 6.84-6.69 (4H, m, Ar*H*), 5.98 (2H, ddt, *J* = 17.2, 10.5, 5.3 Hz, 2 x C*H*=CH_2), 5.22-5.14 (4H, m, 2 x CH_2=CH), 3.87 (4H, dt, *J* = 5.3, 1.6 Hz, 2 x CH_2NH), 3.76 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 151.8 (C), 143.7 (C), 134.9 (2 x =CH), 116.3 (2 x =CH_2), 115.0 (4 x ArCH), 56.1 (2 x CH_2), 54.1 (CH_3); m/z [FAB$^+$] 203.1 (M^++H, 100 %) [found 203.1319 $C_{13}H_{17}NO$ expected 203.1310].

Diethyl hepta-1,6-diene-4,4-dicarboxylate 70[135]



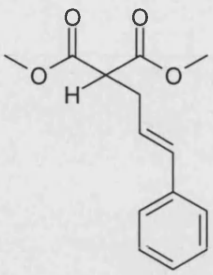
Diethyl malonate **71** (3.0 g, 19 mmol) in dry tetrahydrofuran (30 mL) was added to a solution of sodium hydride (1.5 g, 37 mmol) in dry tetrahydrofuran (40 mL) at 0 °C. The mixture was stirred for 15 minutes, then allyl bromide (2.7 g, 23 mmol) was added dropwise and the solution was stirred for 17 hours. The reaction mixture was quenched with hydrochloric acid (1 M) then diethyl ether (30 mL) and water (30 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with brine (3 x 30 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 1:99) as eluent furnished diethyl hepta-1,6-diene-4,4-dicarboxylate **70** (2.8 g, 62 %). R_f 0.28 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1734 (C=O), 1445 (C-H), 1368 (CH_3), 1217 (C-O), 1145 (C-O); δ_H (270 MHz; $CDCl_3$) 5.79-5.57 (2H, m, 2 x C*H*=CH_2), 5.13-5.03 (4H, m, 2 x CH=CH_2), 4.17 (4H, q, *J* = 7.0 Hz, 2 x C$H_2$$CH_3$), 2.63 (4H, d, *J* = 7.4 Hz, 2 x CH_2CH=), 1.24 (6H, t, *J* = 7.0 Hz, 2x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 170.8 (2 x C), 132.5 (2 x =CH), 119.4 (2 x =CH_2), 61.6 (2 x CH_2), 57.6 (C), 37.1 (2 x CH_2), 14.6 (2 x CH_3); m/z [FAB$^+$] 241.1 (M^++H, 52 %).

Diethyl 1,7-diphenylhepta-1,6-diene-4,4-dicarboxylate 72[136]



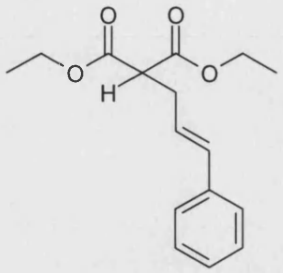
Diethyl malonate **71** (3.2 g, 20 mmol) in dry tetrahydrofuran (30 mL) was added to a solution of sodium hydride (0.95 g, 24 mmol) in dry tetrahydrofuran (30 mL) at 0 °C. The mixture was stirred for 15 minutes, then cinnamyl chloride (3.7 g, 24 mmol) was added dropwise and the solution was stirred for 20 hours. The reaction mixture was quenched with hydrochloric acid (1 M) and partitioned between diethyl ether (30 mL) and water (30 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL) then the combined organics were washed with brine (3 x 30 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. This was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 5:95) as eluent to give diethyl 1,7-diphenylhepta-1,6-diene-4,4-dicarboxylate **72** (4.5 g, 58 %). R_f 0.47 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1729 (C=O), 1495 (C=C), 1448 (C=C), 1367 (CH_3), 1195 (C-O), 967 (CH=CH); δ_H (270 MHz; $CDCl_3$) 7.48-7.03 (10H, m, Ar*H*), 6.47 (2H, d, *J* = 15.5 Hz, 2 x CH=C*H*Ph), 6.10 (2H, dt, *J* = 15.5, 7.5 Hz, 2 x C*H*=CHPh), 4.22 (4H, q, *J* = 7.0 Hz, 2 x CH_2CH_3), 2.85 (4H, d, *J* = 7.5 Hz, 2 x CH_2CH), 1.25 (6H, t, *J* = 7.0 Hz, 2 x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 170.9 (2 x C), 137.3 (2 x C), 134.3 (2 x =CH), 128.7 (4 x ArCH), 127.6 (2 x ArCH), 126.4 (4 x ArCH), 124.2 (2 x =CH), 61.7 (2 x CH_2), 58.3 (C), 37.0 (2 x CH_2), 14.7 (2 x CH_3); m/z [FAB^+] 393.2 (M^++H, 60 %) [found 393.2060 $C_{25}H_{29}O_4$ expected 393.2066].

Dimethyl (3-phenylprop-2-enyl)malonate 73[97]



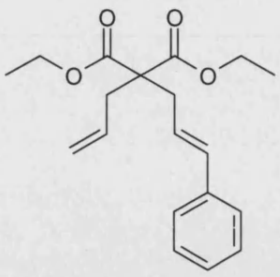
Diethyl malonate **71** (0.47 g, 3.0 mmol) was added dropwise to a solution of sodium methoxide (0.20 g, 3.6 mmol) in methanol (20 mL) at 0 °C. The mixture was stirred for 15 minutes, then cinnamyl chloride (0.59 g, 3.6 mmol) was added dropwise and the solution was stirred for 18 hours. The reaction mixture was quenched with hydrochloric acid (1 M) then diethyl ether (20 mL) and water (20 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 20 mL) then the combined organics were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The yellow residue was then purified by distillation using a Kugelröhr affording dimethyl (3-phenylprop-2-enyl)malonate **73** (0.45 g, 62 %) as a colourless oil. R_f 0.20 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1732 (C=O), 1494 (C=C), 1435 (C=C), 1230 (C-O), 966 (CH=CH); δ_H (270 MHz; $CDCl_3$) 7.34-7.17 (5H, m, Ar*H*), 6.46 (1H, dd, J = 15.8, 2.3 Hz, CH=C*H*Ph), 6.09 (1H, m, C*H*=CHPh), 3.73 (6H, s, 2 x CH_3), 3.52 (1H, t, J = 7.5 Hz, C*H*CH_2), 2.81 (2H, dq, J = 7.5, 1.2 Hz, CHCH_2); δ_C (100 MHz; $CDCl_3$) 169.4 (2 x C), 137.1 (C), 133.1 (=CH), 128.7 (2 x ArCH), 127.6 (ArCH), 126.4 (2 x ArCH), 124.0 (=CH), 52.1 (CH), 32.7 (CH_2), 14.6 (2 x CH_3); m/z [FAB^+] 249.1 (M^++H, 98 %) [found 249.1121 $C_{14}H_{17}O_4$ expected 249.1127].

Diethyl (3-phenylprop-2-enyl)malonate 74[137]



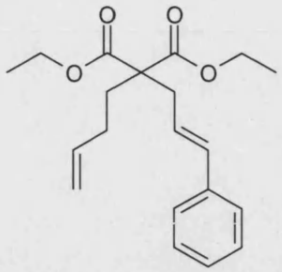
Sodium (0.25 g, 10 mmol) was dissolved in ethanol (20 mL) and added *via* a cannula into a stirring mixture of diethyl malonate **71** (1.6 g, 9.9 mmol) in ethanol (40 mL) at 0 °C. After 15 minutes, cinnamyl chloride (1.7 g, 11 mmol) was added and the solution was stirred at room temperature for 17 hours. The reaction mixture was quenched with water and extracted with dichloromethane (4 x 20 mL). The combined organics were combined and washed with brine (2 x 20 mL), dried with magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil, which was purified by Kugelröhr distillation. Diethyl (3-phenylprop-2-enyl)malonate **74** (1.77 g, 62 %) was afforded as a colourless oil. R_f 0.31 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1732 (C=O), 1448 (C=C), 1369 (CH_3), 1226 (C-O), 1153 (C-O), 967 (CH=CH); δ_H (270 MHz; $CDCl_3$) 7.38-7.14 (5H, m, Ar*H*), 6.47 (1H, d, *J* = 15.7 Hz, CH=C*H*Ph), 6.15 (1H, dt, *J* = 15.7, 7.2 Hz, C*H*=CHPh), 4.20 (4H, q, *J* = 7.2 Hz, 2 x C$H_2$$CH_3$), 3.48 (1H, t, *J* = 7.2 Hz, C*H*CH_2), 2.79 (2H, q, *J* = 7.2 Hz, CH_2CH), 1.25 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 169.0 (2xC), 137.2 (C), 133.0 (=CH), 128.7 (2 x ArCH), 127.6 (ArCH), 126.4 (2 x ArCH), 125.8 (=CH), 61.8 (CH_2), 52.4 (CH), 32.7 (2 x CH_2), 14.6 (2 x CH_3); m/z [FAB^+] 277.0 (M^++H, 100 %).

Diethyl 1-phenylhepta-1,6-diene-4,4-dicarboxylate 67[138]



Diethyl (3-phenylprop-2-enyl)malonate **74** (5.00 g, 18.10 mmol) was added dropwise to a solution of sodium hydride (0.87 g, 22 mmol) in dry tetrahydrofuran (50 mL) at 0 °C. The mixture was stirred for 15 minutes, then allyl bromide (2.6 g, 22 mmol) was added dropwise and the solution was stirred for 6 hours. The reaction mixture was quenched with hydrochloric acid (1 M) then diethyl ether (30 mL) and water (30 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organics were combined and washed with brine (2 x 30 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by distillation using a Kugelröhr gave diethyl 1-phenylhepta-1,6-diene-4,4-dicarboxylate **67** (5.4 g, 98 %) as a colourless oil. R_f 0.53 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1732 (C=O), 1447 (C=C), 1367 (CH_3), 1210 (C-O), 1188 (C-O), 967 (CH=CH); δ_H (270 MHz; $CDCl_3$) 7.33-7.18 (5H, m, Ar*H*), 6.43 (1H, d, *J* = 15.5 Hz, CH=C*H*Ph), 6.03 (1H, dt, *J* = 15.5, 7.6 Hz, C*H*=CHPh), 5.67 (1H, m, C*H*=CH_2), 5.16-5.10 (2H, m, CH_2=CH), 4.23 (4H, q, *J* = 7.2 Hz, 2 x C$H_2$$CH_3$), 2.78 (2H, dd, *J* = 7.6, 1.0 Hz, CH_2CH=CH), 2.68 (2H, d, *J* = 7.6 Hz, CH_2CH=CH_2), 1.24 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 170.9 (2xC), 137.3 (C), 134.1 (=CH), 132.5 (=CH), 128.7 (2 x ArCH), 127.6 (ArCH), 126.4 (2 x ArCH), 124.2 (=CH), 119.5 (=CH_2), 61.7 (CH_2), 58.0 (C), 37.5 (CH_2), 36.6 (2 x CH_2), 14.6 (2 x CH_3); m/z [FAB^+] 317.1 (M^++H, 12 %).

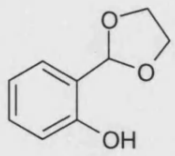
Diethyl 1-phenylocta-1,7-diene-4,4-dicarboxylate 68[82]



Diethyl (3-phenylprop-2-enyl)malonate **74** (0.50 g, 1.8 mmol) was added dropwise to a solution of sodium hydride (87 mg, 2.2 mmol) in dry tetrahydrofuran (10 mL) at 0 °C. The mixture was stirred for 15 minutes, then 4-bromo-1-butene (0.29 g, 2.2 mmol) was added dropwise and the solution was stirred for 17 hours at 45 °C. The reaction mixture was quenched with hydrochloric acid (1 M) then diethyl ether (10 mL) and water (10 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organics were washed with brine (2 x 10 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by distillation using a Kugelröhr giving diethyl 1-phenylocta-1,7-diene-4,4-dicarboxylate **68** (0.37 g, 62 %). R_f 0.37 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1731 (C=O), 1448 (C-H), 1369 (CH_3), 1201 (C-O), 968 ($CH{=}CH_{(trans)}$), 916 ($CH{=}CH_2$), 741 ($CH{=}CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.30-7.18 (5H, m, Ar*H*), 6.44 (1H, d, *J* = 15.5 Hz, CH=C*H*Ph), 6.03 (1H, dt, *J* = 15.5, 7.4 Hz, C*H*=CHPh), 5.77 (1H, m, C*H*=CH_2), 5.02 (1H, d, *J* = 17.1 Hz, $CH_{(trans)}$=CH), 4.95 (1H, d, *J* = 10.1 Hz, $CH_{(cis)}$=CH), 4.18 (4H, dq, *J* = 7.2, 2.0 Hz, 2 x CH_2CH_3), 2.81 (2H, dd, *J* = 7.4, 1.2 Hz, CH_2CH=CH), 2.02 (4H, bs, CH_2CH_2), 1.24 (6H, dt, *J* = 7.2, 2.0 Hz, 2 x CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 170.9 (2 x C), 137.4 (CH=), 136.9 (C), 133.6 (CH=), 128.3 (2 x ArCH), 127.2 (ArCH), 126.0 (2 x ArCH), 123.9 (CH=), 115.0 (CH_2=), 61.3 (CH_2), 57.5 (C), 36.5 (2 x CH_2), 31.9 (CH_2), 28.5 (CH_2), 14.3 (2 x CH_3). m/z [FAB^+] 331.2 (M^++H, 96 %) [found 331.1903 $C_{20}H_{27}O_4$ expected 331.1909].

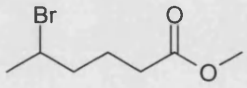
7.1.3 Synthesis of vinyl-supported initiator

2-(2-Hydroxyphenyl)1,3-dioxolane 75[139;140]



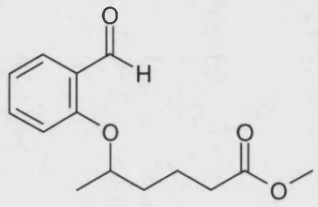
A mixture of salicylaldehyde **78** (2.5 g, 20 mmol), ethylene glycol (3.5 mL, 63 mmol) and a catalytic amount of *p*-toluenesulfonic acid (0.38 g, 2.0 mmol) in toluene (80 mL) was heated under reflux using a Dean Stark apparatus for 24 hours. The solvent was then evaporated and the product was finally distilled with a Kugelröhr at 75 °C under atmospheric pressure to afford compound **75** as a white solid (0.71 g, 21 %). R_f 0.09 (15:85 diethyl ether: hexane); δ_H (400 MHz; $CDCl_3$) 7.77 (1H, s, O*H*), 7.29-7.22 (2H, m, Ar*H*), 6.92-6.88 (2H, m, Ar*H*), 5.94 (1H, s, C*H*O_2), 4.21-4.15 (2H, m, 2 x C$H_a$$H_b$O), 4.10-4.05 (2H, m, 2 x C$H_a$$H_b$O).

Methyl 5-bromohexanoate 79[99]



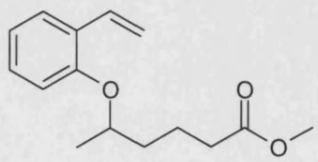
Carbon tetrabromide (2.7 g, 8.2 mmol) in dry tetrahydrofuran (15 mL) was added dropwise to a solution of alcohol **42** (1.0 g, 6.8 mmol), triphenylphosphine (4.3 g, 16 mmol) and pyridine (0.67 mL, 8.2 mmol) in dry tetrahydrofuran (40 mL). The reaction mixture was stirred for 2 hours at room temperature, concentrated under reduced pressure and purified by flash chromatography using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent to afford bromide **79** (1.2 g, 84 %) as a colourless oil. R_f 0.49 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3000-2850 (C-H), 1738 (C=O), 1436 (C-H), 1379 (CH_3), 1198 (C-O); δ_H (270 MHz; $CDCl_3$) 4.10 (1H, sextet, *J* = 7.1 Hz, C*H*CH_3), 3.64 (3H, s, CH_3O), 2.31 (2H, t, *J* = 7.1 Hz, CH_2CO), 1.88-1.75 (4H, m, CHCH_2CH_2), 1.68 (3H, d, *J* = 7.1 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 173.6 (C), 51.8 (CH_3), 50.9 (CH), 40.7 (CH_2), 33.6 (CH_2), 23.7 (CH_3), 23.6 (CH_2); m/z [CI^+] 210.9 (M^++H, 13 %).

Methyl 5-(2-formylphenoxy)hexanoate 76[105]



Potassium carbonate (0.20 g, 1.4 mmol) was added to a solution of salicylaldehyde **78** (0.20 mL, 1.9 mmol) in dry dimethylformamide (5 mL). The mixture was stirred for 1 hour then a solution of bromide **79** (0.20 g, 0.96 mmol) in dry dimethylformamide (2 mL) was added. The reaction mixture was stirred for 17 hours at 50 °C and concentrated under vacuum. Enough water was added to dissolve the solid material and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organics were washed with aqueous sodium hydroxide (1M, 2 x 10 mL), water (2 x 5 mL), then dried with anhydrous magnesium sulfate, filtered concentrated under reduced pressure and purified by flash chromatography using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent, to afford compound **76** as a colourless oil (0.18 g, 72 %). R_f 0.10 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (=CH), 3000-2850 (C-H), 1736 ($C{=}O_{ester}$), 1686 ($C{=}O_{ald}$), 1598 (C=C), 1480 (C=C), 1458 (C-H), 1381 (CH_3), 1241 ($C\text{-}O_{ether}$), 1162 ($C\text{-}O_{ester}$); δ_H (270 MHz; $CDCl_3$) 10.47 (1H, s, C*H*O), 7.82-6.93 (4H, m, Ar*H*), 4.51 (1H, sextet, J = 6.0 Hz, C*H*CH_3), 3.64 (3H, s, CH_3O), 2.35 (2H, t, J = 7.1 Hz, CH_2CO), 1.87-1.68 (4H, m, CHCH_2CH_2), 1.35 (3H, d, J = 6.0 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 189.9 (CHO), 173.7 (C), 160.5 (C), 135.8 (ArCH), 128.3 (ArCH), 125.7 (C), 120.4 (ArCH), 113.7 (ArCH), 74.2 (CH), 51.5 (CH_3), 35.7 (CH_2), 33.7 (CH_2), 20.9 (CH_2), 19.5 (CH_3).

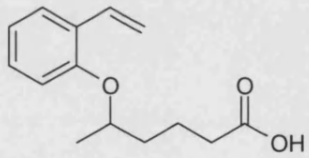
Methyl 5-(2-vinylphenoxy)hexanoate 45[102]



Methyltriphenylphosphonium bromide (1.4 g, 4.0 mmol) and potassium *tert*-butoxide (0.42 g, 3.7 mmol) in tetrahydrofuran (7 mL) were stirred for 1 hour at 0 °C. The aldehyde **76** (0.67 g, 2.7 mmol) in tetrahydrofuran (14 mL) was then added *via* a cannula to the reaction mixture, which was stirred for 17 hours at room temperature. The reaction

mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL) and the combined organics washed with brine (2 x 30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 5:95) as eluent furnished the ester **45** (0.60 g, 91 %). R_f 0.55 (15:85 ethyl acetate: hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 2800-2500 (O-H), 1739 (C=O), 1625 (C=C), 1597 (C=C), 1484 (C=C), 1453 (-CH), 1240 (C-O), 1171 (C-O-C); δ_H (270 MHz; $CDCl_3$) 7.42-6.76 (5H, m, Ar*H* and C*H*=CH_2), 5.64 (1H, dd, *J* = 18.0, 0.7 Hz, $CH_{(trans)}$=CH), 5.15 (1H, dd, *J* = 11.0, 0.7 Hz, $CH_{(cis)}$=CH), 4.31 (1H, sextet, *J* = 5.8 Hz, C*H*CH_3), 3.58 (3H, s, CH_3O), 2.28 (2H, t, *J* = 6.4 Hz, CH_2CO), 1.77-1.54 (4H, m, CHCH_2CH_2), 1.23 (3H, d, *J* = 5.8 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 174.0 (C), 155.2 (C), 131.9 (ArCH), 128.8 (ArCH), 127.9 (C), 126.6 (ArCH), 120.6 (ArCH), 114.0 (=CH_2), 113.8 (=CH), 74.0 (CH), 51.6 (CH_3), 36.0 (CH_2), 34.0 (CH_2), 21.1 (CH_2), 19.8 (CH_3).

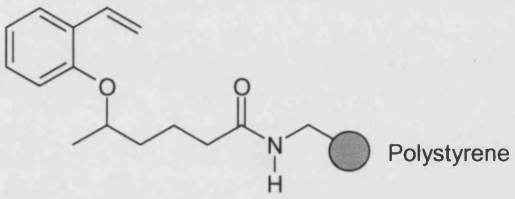
Methyl 5-(2-vinylphenoxy)hexanoic acid 46[89]



Sodium hydroxide (1 M, 3.6 mL, 3.6 mmol) was added dropwise to a stirred solution of methyl 5-(2-vinylphenoxy)hexanoate **45** (0.60 g, 2.4 mmol) in 1,4-dioxane (7 mL) at room temperature and the reaction mixture stirred for 17 hours, then concentrated under vacuum. Diethyl ether (30 mL) and water (30 mL) were added to the resulting oil and the aqueous phase was washed with diethyl ether (3 x 30 mL). The organic phase was extracted with water (3 x 30 mL). The combined aqueous extracts were acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 30 mL). The combined organics were washed with brine (2 x 30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the acid **46** (0.51 g, 89 %) as a pale yellow oil. R_f 0.31 (15:85 ethyl acetate: hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 2800-2500 (O-H), 1708 (C=O), 1625 (C=C), 1597 (C=C), 1484 (C=C), 1453 (-CH), 1240 (C-O); δ_H (270 MHz; $CDCl_3$) 7.43-6.77 (5H, m, Ar*H* and C*H*=CH_2), 5.65 (1H, dq, *J* = 17.6, 1.5 Hz, $CH_{(trans)}$=CH), 5.16 (1H, dd, *J* = 11.0, 1.5 Hz,

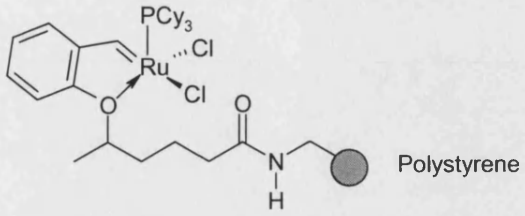
$CH_{(cis)}$=CH), 4.33 (1H, sextet, J = 6.0 Hz, $CHCH_3$), 2.34 (2H, t, J = 7.0 Hz, CH_2CO), 1.82-1.59 (4H, m, $CHCH_2CH_2$), 1.24 (3H, d, J = 6.0 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 179.8 (C), 155.2 (C), 132.1 (ArCH), 128.9 (ArCH), 128.0 (C), 126.8 (ArCH), 120.9 (ArCH), 114.2 (=CH_2), 114.0 (=CH) 74.3 (CH), 36.3 (CH_2), 34.2 (CH_2), 21.2 (CH_2), 20.2 (CH_3); m/z [FAB^+] 235.2 (M^+, 23 %).

5-(2-Vinylphenoxy)hexanoylamino-polystyrene 47



Di-*iso*-propylcarbodiimide (0.60 mL, 4.8 mmol) and 1-hydroxybenzotriazole (0.65 g, 4.8 mmol) were added to a solution of 5-(2-vinylphenoxy)hexanoic acid **46** (1.1 g, 4.8 mmol) in dichloromethane:dimethylformamide (1:1, 2 mL). The reaction mixture was stirred for 10 minutes and then added to the resin (amino methyl resin SS, loading approx. 2.4 $mmol.g^{-1}$) (0.33 g, 0.80 mmol) in dichloromethane:dimethylformamide (1 mL, 1:1). The reaction mixture was stirred for 18 hours by vertical rotation, on a blood rotator. Remaining acid was recovered by washing the resin with dichloromethane. The resin was then washed with sequential portions of dichloromethane, tetrahydrofuran, dimethylformamide, dimethylformamide:methanol (1:1), dimethylformamide, tetrahydrofuran and dichloromethane. The beads were then dried under reduced pressure to obtain the desired resin **47** (0.33 g). (A small portion of the resin was subjected to the Kaiser test[5], which was negative). ν_{max} cm^{-1} (film) 1668 ($C=O_{amide}$).

Aminopolystyrene-supported ruthenium initiator 41

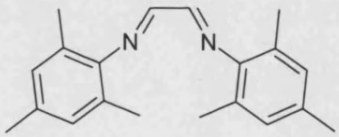


A sonicated solution of Grubbs catalyst (73 mg, 88 μmol) in degassed 1,2-dichloroethane (1 mL) was added to a suspension of 5-(2-vinylphenoxy)hexanoylamino-polystyrene **47** (0.56 g, 0.88 mmol) in 1,2-dichloroethane (2 mL). The reaction mixture was agitated by vertical rotation for two hours at room temperature. The resin was then washed with dichloromethane until the filtrate bacame clear. This entire operation was repeated five times with the new resin being finally dried in a drying pistol to afford the required initiator **41** as brown beads.

7.2 Exploration of initiator substituents

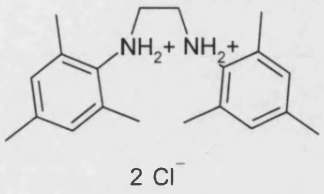
7.2.1 Second generation amino polystyrene and PEGA-supported initiators

1,2-*Bis*-(2,4,6-trimethylphenylimino)ethane 85[90]



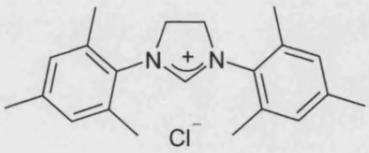
A mixture of 40 % aqueous solution of glyoxal **83** (3.6 g, 25 mmol) was added to a solution of 2,4,6-trimethylphenylamine **84** (7.0 g, 51 mmol) in *n*-propanol (30 mL) at room temperature and the reaction mixture was stirred for 16 hours at room temperature. Water (20 mL) was added, and the resulting yellow precipitate was collected by filtration and dried under vacuum to afford compound **85** as yellow needles (5.4 g, 76 %). mp 157 °C (literature m.p. 157-158 °C)[90]; R_f 0.87 (2:1 diethyl ether:hexane); ν_{max} cm^{-1} (disc), 3100-3000 (=CH), 3000-2850 (C-H), 1617 (C=N), 1476 (-CH), 1374 (CH_3); δ_H (400 MHz; $CDCl_3$) 8.10 (2H, s, 2 x C*H*N), 6.92 (4H, d, J = 0.8 Hz, Ar*H*), 2.30 (6H, s, 2 x CH_3), 2.16 (12H, s, 4 x CH_3); δ_C (100 MHz; $CDCl_3$) 163.6 (6 x C), 134.6 (2 x C), 129.2 (4 x ArCH), 126.8 (2 x CH=N), 21.2 (2 x CH_3), 18.7 (4 x CH_3); m/z [FAB^+] 293.2 (M^++H, 83 %) [found 293.2024 $C_{20}H_{25}N_2$ expected 293.2018].

N,N'-Bis(2,4,6-trimethylphenylamino)ethane dihydrochloride 86[90]



Sodium borohydride (1.5 g, 41 mmol) was slowly added to a solution of 1,2-*bis*(2,4,6-trimethylphenylimino)ethane **85** (2.9 g, 10 mmol) in tetrahydrofuran (40 mL) at 0 °C. The mixture was stirred for 16 hours at room temperature after which ice-water (30 mL) and hydrochloric acid (1M, 30 mL) were added and the resulting white precipitate was collected by filtration and dried in vacuo to afford **86** as a white powder (3.1 g, 85 %). mp 261 °C (literature[90] m.p. >250 °C); R_f 0.25 (1:2 diethyl ether:hexane); ν_{max} cm^{-1} (disc) 3425-3225 (N-H), 3100-3000 (=CH), 3000-2850 (C-H), 1610 (N-H), 1483 (C=C), 1397 (CH_3); δ_H (400 MHz; DMSO-d_6) 6.89 (4H, s, Ar*H*), 3.34 (4H, s, 2 x CH_2N), 2.32 (12H, s, 4 x CH_{3ortho}), 2.20 (6H, s, 2 x CH_{3para}); δ_C (100 MHz; DMSO-d_6) 136.8 (6 x C), 135.5 (2 x C), 131.5 (2 x ArCH), 130.5 (2 x ArCH), 47.9 (2 x CH_2N), 21.2 (2 x CH_3), 19.0 (4 x CH_3); m/z [FAB^+] 296.2 (M^+, 12 %).

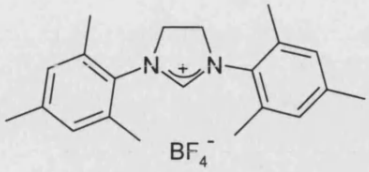
1,3-*Bis*-(2,4,6-trimethylphenyl)imidazolinium chloride 82.HCl[104]



A mixture of *N,N'-bis*-(2,4,6-trimethylphenylamino)ethane dihydrochloride **86** (1.0 g, 2.8 mmol), triethyl orthoformate (10 mL) and two drops of formic acid (90 %) were distilled until the ethanol distillation ceased (~140 °C). Upon cooling to room temperature, a white solid precipitated and was collected by filtration and dried in vacuo affording the imidazolinium salt **82.HCl** (0.85 g, 89 %). R_f 0.59 (1:4 methanol:acetone); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1623 (C-N), 1484 (C=C), 1444 (-CH); δ_H (270 MHz; $CDCl_3$) 9.00 (1H, s, C*H*), 7.08 (4H, s, Ar*H*), 4.43 (4H, s, 2 x CH_2N) 2.34 (12H, s, 4 x CH_{3ortho}), 2.28 (6H, s, 2 x CH_{3para}); δ_C (100 MHz; $CDCl_3$) 160.8 (CH), 140.3 (2 x C), 136.4 (4 x C), 131.5 (2 x C), 130.1 (4 x ArCH), 51.7 (2 x CH_2N), 21.5 (2 x CH_3),

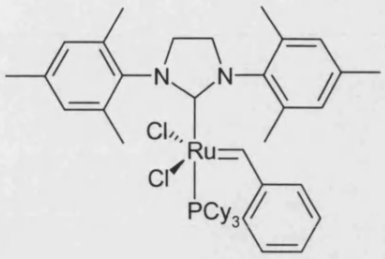
18.1 (4 x CH_3); m/z [FAB^+] 307.2 (M^++H, 100 %) [found 307.2187 $C_{21}H_{27}N_2$ expected 307.2142].

1,3-*Bis*(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate 82.BF_4[90]



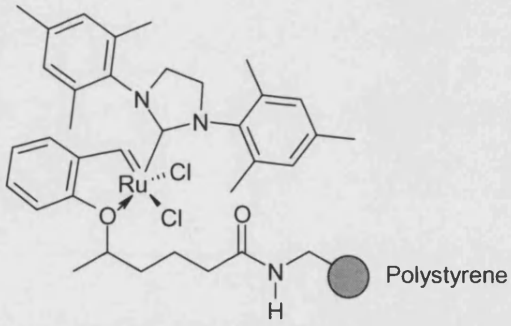
Sodium hydrogen carbonate and ethyl acetate were added to *N,N'-bis*-(2,4,6-trimethylphenylamino)ethane dihydrochloride **86** (2.0 g, 5.7 mmol). The mixture was extracted with ethyl acetate until all the salt changed into oil. The mixture was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Ammonium tetrafluoroborate (0.59 g, 5.7 mmol) was added to this intermediate (1.7 g, 5.7 mmol) followed by triethyl orthoformate (0.84 g, 5.7 mmol) and was heated at reflux for 3 hours then cooled to room temperature. The resulting precipitate was collected by filtration and recrystallised from hot anhydrous ethanol. White crystals of product **82.BF_4** were recovered by vacuum filtration, washed with hexane, and dried under high vacuum (1.5 g, 66 %). mp 292 °C (literature[26] m.p. >250 °C); R_f 0.56 (4:1 dichloromethane:acetone); ν_{max} cm^{-1} (disc), 3100-3000 (=CH), 3000-2850 (C-H), 1629 (C=N), 1486 (-CH), 1394 (CH_3), 852 (C-H); δ_H (400 MHz; DMSO-d_6) 8.98 (1H, s, C*H*N), 7.09 (4H, s, Ar*H*), 4.44 (4H, s, 2 x CH_2N), 2.34 (12H, s, 4 x CH_{3ortho}), 2.29 (6H, s, 2 x CH_{3para}); δ_C (100 MHz; DMSO-d_6) 160.2 (CH), 139.6 (2 x C), 135.4 (4 x C), 130.8 (2 x C), 129.4 (4 x ArCH), 50.9 (2 x CH_2N), 20.5 (2 x CH_3), 17.2 (4 x CH_3); m/z [FAB^+] 307.2 (M^++H, 100 %) [found 307.2186 $C_{21}H_{27}N_2$ expected 307.2142].

Grubbs second generation ruthenium catalyst 7[90]



Potassium *tert*-pentylate in toluene (0.30 mL, 0.59 mmol) was stirred in a two-necked flask under vacuum for two hours. 1,3-*Bis*-(2,4,6-trimethylphenyl)imidazolinium tetrafluoroborate **82.BF$_4$** (0.23 g, 0.59 mmol) in degassed hexane (10 mL) was added and the reaction mixture stirred for 1.5 hours at room temperature. Finally, Grubbs catalyst (0.33 g, 0.39 mmol) was added and the reaction mixture was stirred for 2 hours at 60 °C giving the second generation catalyst **7** (0.29 g, 86 %). R_f 0.42 (1:1 diethyl ether:hexane); δ_H (400 MHz; $CDCl_3$) 19.87 (1H, s, =C*H*) 8.44-7.31 (9H, m, Ar*H*), 2.62 (4H, bs, 2 x CH_2N), 1.90-1.19 (51H, m, 3 x C*H*, 15 x CH_2, 6 x CH_3).

Second generation polystyrene-supported initiator 88



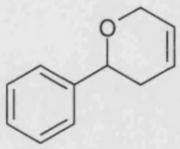
A sonicated solution of second generation Grubbs catalyst **7** (81 mg, 94 μmol) in degassed 1,2-dichloroethane (1mL) was added to a suspension of 5-(2-vinylphenoxy) hexanoylamino-polystyrene **47** (0.59 g, 0.94 mmol) in 1,2-dichloroethane (2 mL). The vessel was sealed to another plastic vessel (role of air-condenser) and heated to 40 °C for 4 hours, followed by washing with dichloromethane until the filtrate was clear. This entire operation was repeated five times. The new resin **88** was finally dried under vacuum to afford the required compound as dark green beads.

Testing of olefin metathesis initiators in ring-closing and cross metathesis:

General method

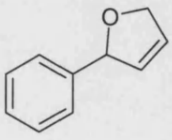
In a 3 mL plastic solid phase synthesis tube, the substrate (~30 mg) in dichloromethane (0.50 mL) was added to the first/second generation amino polystyrene-supported initiator **41/88** (25 mg). The reaction mixture was agitated by vertical rotation at room temperature for 90 minutes then washed with dichloromethane (3 x 5 mL) and the residue was concentrated under reduced pressure. The ^{1}H NMR spectra showed the presence of the product.

6-Phenyl-5,6-dihydro-2*H*-pyran 80[94]



Compound **58** used as starting material. The product was afforded as an oil with a conversion of 97 % (isolated yield: 95 %) with **41** and 100 % (isolated yield: 98 %) with **88**. R_f 0.49 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1643 (C=C), 1493 (C-H), 1090 (C-O), 739 (CH=CH$_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.39-7.27 (5H, m, Ar*H*), 5.91 (1H, m, OCH$_2$C*H*=), 5.81 (1H, m, CHCH$_2$C*H*=), 4.55 (1H, dd, *J* = 9.9, 4.0 Hz, C*H*O), 4.39-4.36 (2H, m, OC*H*$_2$CH), 2.43-2.16 (2H, m, CHC*H*$_2$CH); δ_C (100 MHz; $CDCl_3$) 142.7 (C), 128.6 (2 x ArCH), 127.7 (ArCH), 126.6 (CH=), 126.1 (2 x ArCH), 124.6 (CH=), 76.0 (CH), 66.9 (CH_2), 33.3 (CH_2); m/z [FAB$^+$] 159.0 (M$^+$-H, 10 %).

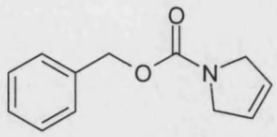
2-Phenyl-2,5-dihydrofuran 61[141]



Compound **62** used as starting material. The product was afforded as an oil with a conversion of 61 % with **41** and 99 % with **88**. ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1491 (C=C), 1454 (C=C), 1063 (C-O), 700 (CH=CH$_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.37-7.26 (5H, m, Ar*H*), 6.06-6.03 (1H, m, C*H*CH=), 5.92-5.88 (1H, m, CHC*H*=), 5.82-5.72 (1H, m, CH$_2$C*H*=), 4.92-4.76 (2H, m, C*H*$_2$CH=); δ_C (100 MHz;

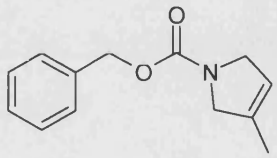
$CDCl_3$) 142.2 (C), 130.1 (CH=), 128.7 (2 x ArCH), 128.0 (ArCH), 126.8 (CH=), 126.6 (2 x ArCH), 88.2 (CH), 76.2 (CH_2).

Benzyl 2,5-dihydropyrrole-1-carboxylate 55[142]



Compound **54** used as starting material. The product was afforded as an oil with a conversion of 92 % (isolated yield: 90 %) with **41** and 98 % (isolated yield: 95 %) with **88**. R_f 0.49 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1706 (C=O), 1624 (C=C), 1421 (C-H), 1363 (CH_3), 1210 (C-O), 769 ($CH=CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.37-7.26 (5H, m, Ar*H*), 5.78 (2H, dd, *J* = 7.9 Hz, CH_2CH=), 5.16 (2H, s, CH_2O), 4.22-4.16 (4H, m, CH_2CH=); δ_C (100 MHz; $CDCl_3$) 154.7 (C), 137.1 (C), 128.7 (2 x ArCH), 128.1 (ArCH), 126.0 (2 x CH=), 125.8 (2 x ArCH), 67.1 (CH_2), 53.8 (CH_2), 53.3 (CH_2); m/z [FAB^+] 204.1 (M^++H, 26 %) [found 204.1016 $C_{12}H_{14}NO_2$ expected 204.1025].

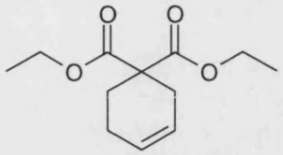
Benzyl 3-methyl-2,5-dihydropyrrole-1-carboxylate 90[143]



Compound **89** used as starting material. The product was afforded as an oil with a conversion of 10 % (isolated yield: 13 %) with **41** and 96 % (isolated yield: 97 %) with **88**. R_f 0.53 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1706 (C=O), 1665 (C=C), 1418 (C-H), 1363 (CH_3), 1106 (C-O), 768 ($CH=CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.37-7.26 (5H, m, Ar*H*), 5.36 (1H, m, CH_2CH=), 5.15 (2H, s, CH_2O), 4.16-4.05 (4H, m, CH_2N), 1.75-1.73 (3H, 2 x s, $CH_{3(A\ and\ B)}$); δ_C (100 MHz; $CDCl_3$) 154.7(C), 137.2 (C), 135.5 ($C_{(A)}$), 135.3 ($C_{(B)}$), 128.7 (2 x $ArCH_{(A)}$), 128.2 (2 x $ArCH_{(B)}$), 128.1 (ArCH), 128.0 (2 x $ArCH_{(A)}$), 127.9 (2x$ArCH_{(B)}$), 119.6 ($CH=_{(A)}$), 119.4 ($CH=_{(B)}$), 67.1 ($CH_{2(A)}$), 67.0 ($CH_{2(B)}$), 56.8 ($CH_{2(A)}$), 56.4 ($CH_{2(B)}$), 54.1 ($CH_{2(A)}$), 53.7 ($CH_{2(B)}$), 17.8 ($CH_{3(A)}$), 14.7 ($CH_{3(B)}$). m/z [FAB^+] 218.1 (M^++H, 64 %) [found 218.1174

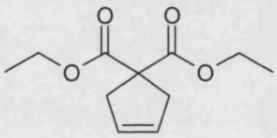
$C_{13}H_{16}NO_2$ expected 218.1181]. (additional peaks in ^1H and ^{13}C spectra due to restricted rotation of C-N bond, two rotamers observed labelled as A and B).

Cyclohex-3-ene-1,1-dicarboxylic acid diethyl ester 91[60]



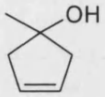
Compound **68** used as starting material. The product was afforded as a oil with a conversion of 42 % with **41** and 89 % with **88**. R_f 0.53 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3000-2850 (C-H), 1733 (C=O), 1446 (C-H), 1367 (CH_3), 1201 (C-O), 742 ($CH{=}CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 5.66 (2H, bs, C*H*=C*H*), 4.19 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 4.17 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 2.54 (2H, bs, $CCH_2CH{=}$), 2.21-2.00 (4H, m, $CH_2CH_2CH{=}$), 1.23 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 171.7 (2 x C), 126.3 (CH=), 124.2 (CH=), 61.6 (CH_2), 53.3 (C), 30.8 (2 x CH_2), 27.8 (CH_2), 22.7 (CH_2), 14.5 (2 x CH_3); m/z [FAB^+] 213.1 (M^+, 26 %).

Cyclopent-3-ene-1,1-dicarboxylic acid diethyl ester 92[144]



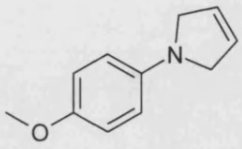
Compound **70** used as starting material. The product was afforded as an oil with a conversion of 36 % with **41** and 83 % with **88**. R_f 0.43 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3000-2850 (C-H), 1732 (C=O), 1644 (C=C), 1446 (C-H), 1367 (CH_3), 1255 (C-O), 735 ($CH{=}CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 5.59 (2H, s, $CH_2CH{=}$), 4.18 (4H, q, *J* = 7.2 Hz, 2 x CH_2CH_3), 3.00 (4H, s, 2 x $CH_2CH{=}$), 1.24 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 172.3 (2 x C), 128.0 (2 x CH=), 61.9 (2 x CH_2), 59.2 (C), 41.2 (2 x CH_2), 14.5 (2 x CH_3); m/z [FAB^+] 213.1 (M^++H, 36 %).

1-Methylcyclopent-3-enol 94[145]



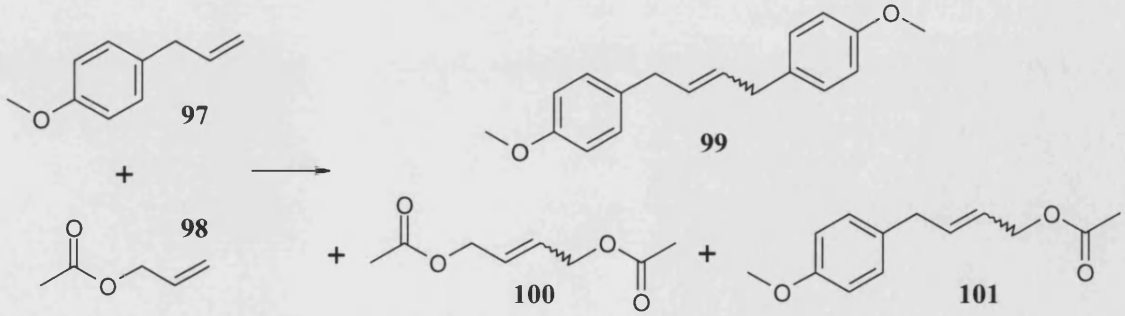
Compound **93** used as starting material. The reaction was carried out in deuterated chloroform with a conversion of 0 % with **41** and 68 % (isolated yield: 50 %) with **88** (product very volatile). δ_H (270 MHz; $CDCl_3$) 5.66 (2H, s, 2 x CH_2CH=), 2.43 (4H, s, 2 x CH_2CH=), 1.78 (1H, bs, O*H*), 1.41 (3H, s, CH_3).

1-(4-Methoxyphenyl)-2,5-dihydro-1*H*-pyrrole 81



Compound **64** used as starting material. The product was afforded as an oil with a conversion of 55 % with **41** and 44 % with **88**. (lit. solid m.p. 118 °C); R_f 0.77 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1641 (C=C), 1515 (C=C), 1185 (C-O), 721 ($CH=CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.00-6.42 (4H, m, ArH), 5.94 (2H, s, CH=CH), 4.08 (4H, s, CH_2CH=), 3.76 (3H, s, CH_3O); δ_C (100 MHz; $CDCl_3$) 151.6 (C), 143.6 (C), 122.4 (2 x ArCH), 119.9 (2 x ArCH), 110.1 (2 x CH=), 55.9 (CH_3), 54.0 (2 x CH_2); m/z [FAB^+] 176.1 (M^++H, 15 %).

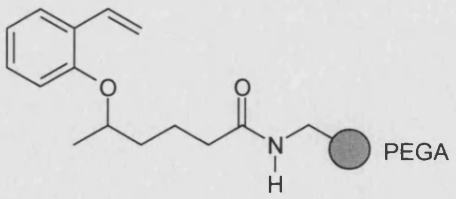
Olefin Cross-metathesis of prop-2-enyl anisole 97 and prop-2-enyl acetate 98.



Compounds **97** and **98** used as starting materials. Product **99**,[146] *cis/trans* 1,4-*bis*(4-methoxyphenyl)-2-butene was afforded as an oil with a isolated yield of 33 % with **41** and 1 % (*Z*:*E* 18:82) with **88**. R_f 0.43 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1610 (C=C), 1510 (C=C), 1243 (C-O), 970 ($CH=CH_{(trans)}$), 815 ($CH=CH_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.13-7.06 (4H, m, Ar*H*), 6.85-

6.80 (4H, m, Ar*H*), 6.67-6.60 (2H, m, C*H*=C$H_{(cis)}$ and C*H*=C$H_{(trans)}$), 3.78 (6H, s, CH_3O), 3.44 (0.8H, d, *J* = 5.3 Hz, CH_2CH$_{(cis)}$=), 3.29 (3.2H, d, *J* = 5.3 Hz, CH_2CH$_{(trans)}$=); δ_C (100 MHz; $CDCl_3$) 158.0 (2 x C), 133.0 (2 x C), 130.7 (4 x ArCH), 129.6 (4 x ArCH), 114.0 (2 x CH=), 55.6 (2 x CH_3), 38.4 (2 x CH_2). Product **100**, *cis/trans* 1,4-diacetoxy-but-2-ene was afforded as an oil with a isolated yield of 45 % with **41** and 27 % (*Z*:*E* 12:88) with **88**. R_f 0.10 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3000-2850 (C-H), 1740 (C=O), 1444 (C-H), 1367 (CH_3), 1228 (C-O), 969 (CH=CH$_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 5.86-5.83 (1.8H, m, C*H*=C$H_{(trans)}$), 5.75-5.72 (0.2H, m, C*H*=C$H_{(cis)}$), 4.66 (0.4H, d, *J* = 5.2 Hz, CH_2CH$_{(cis)}$=), 4.57-4.55 (3.6H, m, CH_2CH$_{(trans)}$=), 2.07 (6H, s, CH_3CO); δ_C (100 MHz; $CDCl_3$) 170.8 (2 x C), 128.2 (2 x CH=), 64.2 (2 x CH_3), 21.4 (2 x CH_2). And finally product **101**, *cis/trans* 4-(4-methoxyphenyl)but-2-enyl acetate was afforded as an oil with a isolated yield of 30 % with **41** and 45 % (*Z*:*E* 9:91) with **88**. R_f 0.25 (15:85 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1739 (C=O), 1611 (C=C), 1512 (C=C), 1442 (C-H), 1363 (CH_3), 1246 (C-O), 1034 (C-O), 972 (CH=CH$_{(trans)}$), 819 (CH=CH$_{(cis)}$); δ_H (270 MHz; $CDCl_3$) 7.08 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.83 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.89 (1H, dt, *J* = 15.2, 6.5 Hz, OCH_2C*H*=), 5.59 (1H, dt, *J* = 15.2, 6.5 Hz, PhCH_2C*H*=), 4.72 (0.2H, d, *J* = 6.5 Hz, OCH_2CH$_{(cis)}$=), 4.53 (1.8H, d, *J* = 6.5 Hz, OCH_2CH$_{(trans)}$=), 3.78 (3H, s, CH_3O), 3.40 (0.2H, d, *J* = 6.5 Hz, PhCH_2CH$_{(cis)}$=), 3.33 (1.8H, d, *J* = 6.5 Hz, PhCH_2CH$_{(trans)}$=), 2.07 (0.3H, s, CH_3CO$_{(cis)}$), 2.05 (2.7H, s, CH_3CO$_{(trans)}$); δ_C (100 MHz; $CDCl_3$) 171.0 (C), 158.2 (C), 135.2 (CH=), 131.7 (C), 129.7 (2 x ArCH), 125.1 (CH=), 114.1 (2 x ArCH), 65.3 (CH_2), 55.6 (CH_3), 38.1 (CH_2), 21.5 (CH_3).

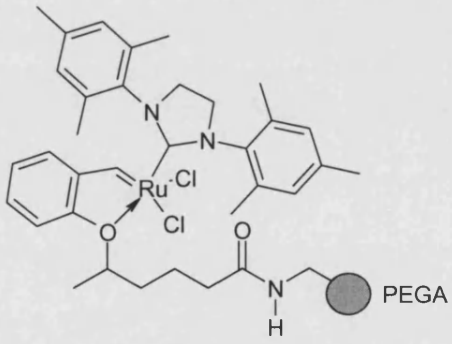
5-(2-Vinylphenoxy)hexanoylamino-PEGA 103



Amino PEGA resin pre-swollen in methanol (2.5 g) was washed with dimethylformamide (2 x 15 mL), tetrahydrofuran (2 x 15 mL), dichloromethane (2 x 15 mL) and dried under vacuum giving dry amino PEGA resin (0.49 g) which was left 1 hour to swell in dimethylformamide (4 mL). In a reaction vessel, di-*iso*-propylcarbodiimide (0.16 mL, 1.0 mmol) and 1-hydroxybenzotriazole (0.14 g, 1.0 mmol) were added to a solution of 5-(2-

vinylphenoxy)hexanoic acid **46** (0.24 g, 1.0 mmol) in dimethylformamide (4 mL). The reaction mixture was stirred for 10 minutes and then added to the pre-swollen resin in dimethylformamide. The reaction mixture was stirred for 24 hours by vertical rotation, on a blood rotator. The resin was washed dimethylformamide (7 x 15 mL) and dichloromethane (3 x 15 mL). A solution of triethylamine (0.72 g, 7.1 mmol) and dimethylaminopyridine (74 mg, 0.61 mmol) in dichloromethane (3 mL) was added to the resin, followed by addition of acetic anhydride (0.62 g, 6.1 mmol) in dichloromethane (1 mL). The resulting mixture was stirred for 20 hours by vertical rotation, on a blood rotator. The resin was washed with dichloromethane (3 x 15 mL), dimethylformamide (3 x 15 mL), water (3 x 15 mL), dimethylformamide (3 x 15 mL), dichloromethane (3 x 15 mL) and diethyl ether (3 x 15 mL). The resin was dried in a drying pistol to obtain the desired resin **103** (0.48 g). (A small portion of the resin was subjected to the Kaiser test, which was negative). ν_{max} cm^{-1} (film) 1669 ($C{=}O_{amide}$).

Second generation PEGA-supported initiator 104



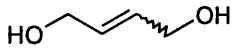
A sonicated solution of second generation Grubbs catalyst **7** (12 mg, 14 μmol) in degassed 1,2-dichloroethane (1 mL) was added to a suspension of 5-(2-vinylphenoxy)hexanoylamino-PEGA **103** (0.48 g, 0.14 mmol) in 1,2-dichloroethane (2 mL). The vessel was sealed to another plastic vessel (role of air-condenser) and heated to 40 °C for 4 hours, followed by washing with dichloromethane until the filtrate was clear. This entire operation was repeated five times. The new resin **104** was finally dried under vacuum to afford the required compound as green beads. ICP-AES: Ru ($mmol_{Ru}/g_{initiator}$) = 0.109.

Testing of olefin metathesis initiators in ring-closing and cross metathesis with initiator:

General method:

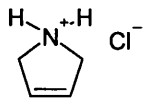
To a 3 mL plastic solid phase synthesis tube, containing the amino polystyrene-supported initiator **104** (25 mg) was added the substrate (~30 mg) in D_2O/methanol (0.50 mL). The reaction mixture was agitated by vertical rotation at room temperature for 90 minutes. The mixture was washed with D_2O or methanol (3 x 5 mL) and the residue was concentrated under reduced pressure.

But-2-ene-1,4-diol 160



Prop-2-en-1-ol **106** used as starting material. The product was afforded as an oil with a conversion of 42 % (isolated yield: 40 %) in methanol and 51 % (isolated yield: 51 %) in D_2O. R_f 0.16 (3:1 ethyl acetate:hexane); δ_H (270 MHz; $CDCl_3$) 5.82- (2H, m, C*H*=C*H*), 4.06-4.04 (4H, m, 2 x CH_2CH=), 1.61 (2H, bs, 2 x O*H*).

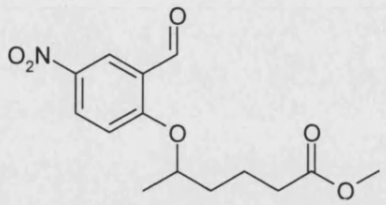
2,5-dihydro-1*H*-pyrrole hydrochloride salt 102



Diprop-2-enylamine chloride salt **69** used as starting material. The product was afforded as a white solid with a conversion of 50 % (isolated yield: 47 %) in methanol and 3 % in D_2O. R_f 0.38 (4:1 dichloromethane:methanol); δ_H (270 MHz; $CDCl_3$) 9.70 (2H, bd, NH_2), 6.02-5.87 (2H, m, C*H*=C*H*), 3.98-4.06 (4H, m, 2xCH_2CH=); m/z [FAB$^+$] 69.9 (M^+, 100 %).

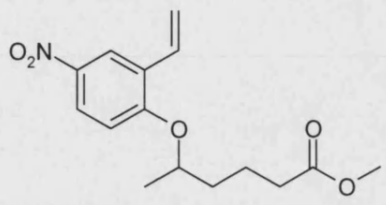
7.2.2 Nitro and methoxy substituted analogues

Methyl 5-(2-formyl-4-nitrophenoxy)hexanoate 109[105]



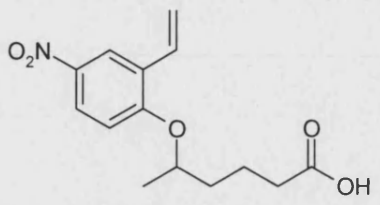
Potassium carbonate (0.26 g, 1.9 mmol) was added to a solution of 2-hydroxy-5-nitro-benzaldehyde (0.20 g, 1.2 mmol) in dry dimethylformamide (5 mL). The mixture was stirred for 1 hour then a solution of methyl 5-bromohexanoate **79** (0.20 g, 0.96 mmol) in dry dimethylformamide (3 mL) was added. The reaction mixture was stirred for 17 hours at 60 °C then concentrated under vacuum. The resulting residue was dissolved in water (30 mL) and was extracted with diethyl ether (3 x 20 mL). The combined organics were washed with sodium hydroxide (1M, 2 x 20 mL), water (20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent afforded compound **109** as a colourless oil (0.10 g, 53 %). R_f 0.20 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1738 (C=O), 1608 (C=C), 1520 (C=C), 1480 (C=C), 1274 (C-O), 1173 (C-O); δ_H (270 MHz; $CDCl_3$) 10.44 (1H, s, C*H*O), 8.68 (1H, d, *J* = 2.8 Hz, Ar*H* C_6), 8.38 (1H, dd, *J* = 9.2, 2.8 Hz, Ar*H* C_5), 7.07 (1H, d, *J* = 9.2 Hz, Ar*H* C_3), 4.73-4.53 (1H, m, CH_3CH), 3.64 (3H, s, CH_3O), 2.37 (2H, t, *J* = 6.9 Hz, CH_2CO), 1.91-1.64 (4H, m, $CHCH_2CH_2$), 1.43 (3H, d, *J* = 6.2 Hz, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 187.6 (CHO), 173.5 (C), 164.3 (C), 140.9 (C_{NO2}), 130.5 (ArCH), 125.1 (C), 124.7 (ArCH), 113.6 (ArCH), 75.9 (CH), 52.0 (CH_3), 35.4 (CH_2), 33.4 (CH_2), 20.7 (CH_2), 19.3 (CH_3); m/z [FAB$^+$] 296.2 (M^++H, 15%) [found 296.1136 $C_{14}H_{18}NO_6$ expected 296.1134].

Methyl 5-(4-nitro-2-vinylphenoxy)hexanoate 111[102]



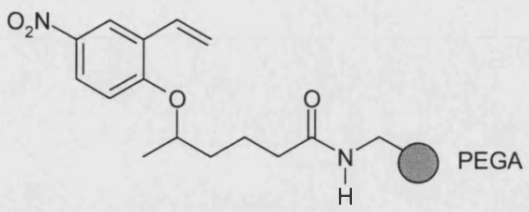
Methyltriphenylphosphonium bromide (0.35 g, 0.99 mmol) and potassium *tert*-butoxide (0.10 g, 0.88 mmol) in tetrahydrofuran (2 mL) were stirred for 1 hour at 0 °C. The aldehyde **109** (0.19 g, 0.63 mmol) in tetrahydrofuran (4 mL) was then added *via* a cannula and the reaction mixture which was stirred for 17 hours at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent furnished the ester **111** (0.10 g, 55 %). R_f 0.54 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1737 (C=O), 1607 (C=C), 1515 (C=C), 1483 (C=C), 1271 (C-O), 1173 (C-O), 988 ($CH=CH_2$); δ_H (270 MHz; $CDCl_3$) 8.35 (1H, d, *J* = 2.7 Hz, Ar*H* C_6), 8.10 (1H, dd, *J* = 9.2, 2.7 Hz, Ar*H* C_5), 6.98 (1H, dd, *J* = 17.7, 11.1 Hz, $CH=CH_2$), 6.88 (1H, d, *J* = 9.2 Hz, Ar*H* C_3), 5.84 (1H, dd, *J* = 17.7, 0.7 Hz, $CH_{(trans)}=CH$), 5.38 (1H, dd, *J* = 11.1, 0.7 Hz, $CH_{(cis)}=CH$), 4.53 (1H, sextet, *J* = 5.5 Hz, $CHCH_3$), 3.65 (3H, s, CH_3O), 2.35 (2H, t, *J* = 6.9 Hz, CH_2CO), 1.89-1.64 (4H, m, $CHCH_2CH_2$), 1.37 (3H, d, *J* = 5.5 Hz, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 173.7 (C), 160.0 (C), 141.2 (C_{NO2}), 130.2 (ArCH), 128.3 (C), 124.8 (ArCH), 122.6 (ArCH), 117.1 ($=CH_2$), 112.3 (=CH), 75.1 (CH), 52.0 (CH_3), 35.4 (CH_2), 33.4 (CH_2), 20.7 (CH_2), 19.3 (CH_3); m/z [FAB^+] 294.2 (M^++H, 12%) [found 294.1339 $C_{15}H_{20}NO_5$ expected 294.1341].

5-(4-Nitro-2-vinylphenoxy)hexanoic acid 113



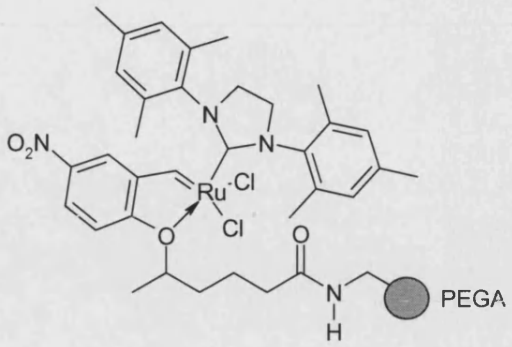
Aqueous sodium hydroxide (1 M, 0.30 mL, 0.30 mmol) was added to a stirred solution of methyl 5-(-4-nitro-2-vinylphenoxy)hexanoate **111** (75 mg, 0.26 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred for 20 hours and then concentrated under vacuum. The residue was partitioned between diethyl ether (10 mL) and water (10 mL) and the aqueous phase was further extracted with diethyl ether (3 x 10 mL). The aqueous phase was acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 10 mL). The combined organics were washed with brine (2 x 10 mL), dried over anhydrous magnesium sulfate, filtered then concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent gave the acid **113** (48 mg, 68 %) as a pale yellow oil. R_f 0.71 (3:1 ethyl acetate:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1708 (C=O), 1582 (C=C), 1515 (C=C), 1483 (C=C), 1256 (C-O), 922 ($CH=CH_2$); δ_H (270 MHz; $CDCl_3$) 8.34 (1H, d, J = 3.0 Hz, Ar*H* C_6), 8.10 (1H, dd, J = 9.2, 3.0 Hz, Ar*H* C_5), 6.97 (1H, dd, J = 17.8 and 11.3 Hz, $CH=CH_2$), 6.88 (1H, d, J = 9.2 Hz, Ar*H* C_3), 5.85 (1H, d, J = 17.8 Hz, $CH_{(trans)}=CH$), 5.39 (1H, d, J = 11.3 Hz, $CH_{(cis)}=CH$), 4.53 (1H, sextet, J = 6.0 Hz, $CHCH_3$), 2.40 (2H, t, J = 6.9 Hz, CH_2CO), 1.91-1.61 (4H, m, $CHCH_2CH_2$), 1.37 (3H, d, J = 6.0 Hz, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 179.3 (C), 159.9 (C), 141.3 (C_{NO2}), 130.1 (ArCH), 128.4 (C), 124.8 (ArCH), 122.6 (ArCH), 117.2 ($=CH_2$), 112.3 (=CH), 75.1 (CH), 35.9 (CH_2), 34.0 (CH_2), 20.9 (CH_2), 19.9 (CH_3); m/z [FAB^+] 280.1 (M^++H, 64 %) [found 280.1178 $C_{14}H_{18}NO_5$ expected 280.1185].

5-(4-Nitro-2-vinylphenoxy)hexanoylamino-PEGA 115



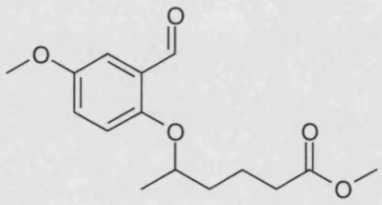
Amino PEGA resin pre-swollen in methanol (2.5 g) was washed with dimethylformamide (2 x 15 mL), tetrahydrofuran (2 x 15 mL), dichloromethane (2 x 15 mL) and dried under vacuum to give dry amino PEGA resin (0.31 g) which was left 1 hour to swell in dimethylformamide (4 mL). In a reaction vessel, di-*iso*-propylcarbodiimide (0.10 mL, 0.65 mmol) and 1-hydroxybenzotriazole (0.09 g, 0.65 mmol) were added to a solution of 5-(4-nitro-2-vinylphenoxy)hexanoic acid **113** (0.18 g, 0.65 mmol) in dimethylformamide (2.5 mL). The reaction mixture was stirred for 15 minutes and added to the pre-swollen resin in dimethylformamide. The reaction mixture was stirred for 22 hours by vertical rotation, and washed with sequential portions of dimethylformamide (7 x 15 mL) and dichloromethane (3 x 15 mL). A solution of triethylamine (0.62 mL, 4.4 mmol) and dimethylaminopyridine (46 mg, 0.37 mmol) in dichloromethane (3 mL) was added to the resin, followed by addition of acetic anhydride (0.38 g, 3.7 mmol) in dichloromethane (1 mL). The resulting mixture was stirred for 24 hours by vertical rotation, and washed with sequential portions of dichloromethane (3 x 15 mL), dimethylformamide (3 x 15 mL), water (3 x 15 mL), dimethylformamide (3 x 15 mL), dichloromethane (3 x 15 mL) and diethyl ether (3 x 15 mL). The resin was then dried in a drying pistol to obtain the desired resin **115** (0.48 g). (A small portion of the resin was subjected to the Kaiser test, which was negative). ν_{max} cm^{-1} (film) 1730 ($C{=}O_{amide}$).

Second generation PEGA-supported initiator nitro analogue 117



A sonicated solution of second generation Grubbs catalyst **7** (15 mg, 17 μmol) in degassed 1,2-dichloroethane (1 mL) was added to a suspension of 5-(4-nitro-2-vinylphenoxy)hexanoylamino-PEGA **115** (0.47 g, 0.17 mmol) in 1,2-dichloroethane (3 mL). The vessel was sealed to another plastic vessel (role of air-condenser) and heated to 40 °C for 4 hours, followed by washing with dichloromethane until the filtrate was clear. This entire operation was repeated five times. The new resin was finally dried under vacuum to afford the required compound **117** as brown beads. ICP-AES: Ru ($mmol_{Ru}/g_{initiator}$) = 0.078.

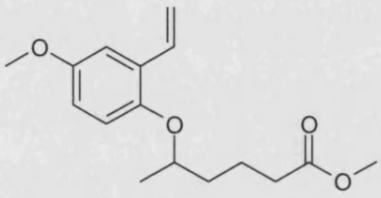
Methyl 5-(2-formyl-4-methoxyphenoxy)hexanoate 110[105]



Potassium carbonate (0.26 g, 1.9 mmol) was added to a solution of 2-hydroxy-5-methoxybenzaldehyde (0.29 g, 1.9 mmol) in dry dimethylformamide (5 mL). After 1 hour, a solution of methyl 5-bromohexanoate **79** (0.20 g, 0.96 mmol) in dry dimethylformamide (3 mL) was added and the reaction mixture was stirred for a further 17 hours at room temperature, which was then concentrated under vacuum. The resulting residue was dissolved in water and extracted with diethyl ether (3 x 20 mL). The combined organics were washed with sodium hydroxide (1M, 20 mL), water (20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 15:85) as eluent and compound **110** was afforded as a

colourless oil (0.19 g, 70 %). R_f 0.44 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1737 (C=O), 1611 (C=C), 1491 (C=C), 1394 (CH_3), 1217 (C-O), 1160 (C-O); δ_H (270 MHz; $CDCl_3$) 10.42 (1H, s, C*H*O), 7.29 (1H, d, *J* = 3.2 Hz, Ar*H* C_6), 7.09 (1H, dd, *J* = 9.2, 3.2 Hz, Ar*H* C_5), 6.92 (1H, d, *J* = 9.2 Hz, Ar*H* C_3), 4.41 (1H, sextet, *J* = 6.0 Hz, CH_3CH), 3.78 (3H, s, CH_3OPh), 3.64 (3H, s, CH_3O), 2.35 (2H, t, *J* = 7.0 Hz, CH_2CO), 1.87-1.63 (4H, m, $CHCH_2CH_2$), 1.31 (3H, d, *J* 6.0, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 189.8 (CHO), 173.7 (C), 155.1 (C), 153.5 (C), 126.1 (C), 123.8 (ArCH), 116.3 (ArCH), 109.8 (ArCH), 75.3 (CH), 55.8 (CH_3), 51.5 (CH_3), 35.8 (CH_2), 33.8 (CH_2), 20.9 (CH_2), 19.6 (CH_3); m/z [FAB^+] 281.1 (M^++H, 20 %) [found 281.1317 $C_{15}H_{21}O_5$ expected 281.1389].

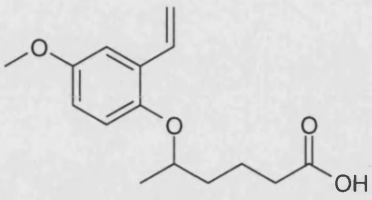
Methyl 5-(4-methoxy-2-vinylphenoxy)hexanoate 112[102]



Methyltriphenylphosphonium bromide (6.9 g, 19 mmol) and potassium *tert*-butoxide (2.0 g, 17.9 mmol) in tetrahydrofuran (50 mL) were stirred for 45 minutes at 0 °C. The aldehyde **110** (3.6 g, 13 mmol) in tetrahydrofuran (25 mL) was then added *via* a cannula into the reaction mixture which was stirred for 20 hours at room temperature. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic phases were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 20:80) as eluent furnished the ester **112** (3.0 g, 85 %). mp 74 °C; R_f 0.59 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1738 (C=O), 1626 (C=C), 1490 (C=C arom), 1377 (CH_3), 1214 (C-O), 1057 (C-O), 910 ($CH=CH_2$); δ_H (400 MHz; $CDCl_3$) 7.07 (1H, dd, *J* = 17.6, 11.2 Hz, $CH=CH_2$), 7.07 (1H, d, *J* = 3.0 Hz, Ar*H* C_6), 6.84 (1H, d, *J* = 9.0 Hz, Ar*H* C_3), 6.80 (1H, dd, *J* = 9.0, 3.0 Hz, Ar*H* C_5), 5.74 (1H, dd, *J* = 17.6, 1.3 Hz, $CH=CH_{(trans)}$), 5.28 (1H, dd, *J* = 11.2, 1.3 Hz, $CH=CH_{(cis)}$), 4.30 (1H, sextet, *J* = 6.0 Hz, $CHCH_3$), 3.82 (3H, s, CH_3OPh), 3.70 (3H, s, CH_3O), 2.39 (2H, t, *J* = 7.3 Hz, CH_2CO), 1.90-1.63 (4H, m, $CHCH_2CH_2$), 1.30 (3H, d, *J* = 6.0 Hz, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 174.0 (C), 153.8 (C), 149.4 (C), 131.8 (ArCH), 129.1

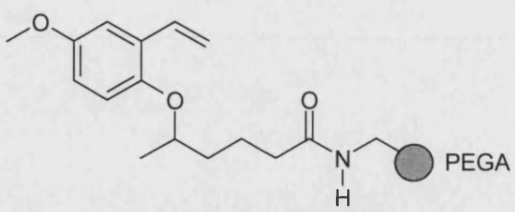
(C), 116.3 (ArCH), 114.2 (=CH_2), 114.1 (=CH), 111.2 (ArCH), 75.4 (CH), 55.7 (CH_3), 51.6 (CH_3), 36.0 (CH_2), 34.0 (CH_2), 21.1 (CH_2), 19.8 (CH_3); m/z [FAB^+] 279.2 (M^+, 25%) [found 279.1591 $C_{16}H_{23}O_4$ expected 279.1596].

5-(4-Methoxy-2-vinylphenoxy)hexanoic acid 114



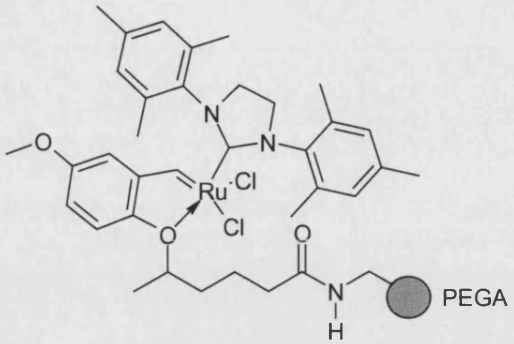
Aqueous sodium hydroxide (1 M, 16 mL, 16 mmol) was added to a solution of methyl 5-(4-methoxy-2-vinylphenoxy)hexanoate **112** (3.0g, 11 mmol) in 1,4-dioxane (40 mL) at room temperature. The reaction mixture was stirred for 17 hours, concentrated under vacuum and dichloromethane (30 mL) and water (30 mL) were added. The aqueous phase was washed with dichloromethane (3 x 30 mL) and the organic phase was washed with water (30 mL). The combined aqueous phases were acidified with hydrochloric acid (1 M) and extracted with diethyl ether (3 x 40 mL). The organic phase was washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the acid **114** (2.8 g, 97 %) as a yellow oil. R_f 0.38 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3500-2500 (O-H), 3100-3000 (ArH), 3000-2850 (C-H), 1708 (C=O), 1625 (C=C), 1490 (C=C), 1420 (C-H), 1378 (CH_3), 1214 (C-O), 1057 (C-O); δ_H (270 MHz; $CDCl_3$) 7.02 (1H, dd, J = 17.7, 11.1 Hz, CH_2=C*H*), 7.02 (1H, d, J = 2.9 Hz, Ar*H* C_6), 6.80 (1H, d, J = 8.9 Hz, Ar*H* C_3), 6.74 (1H, dd, J = 8.9, 2.9 Hz, Ar*H* C_5), 5.69 (1H, dd, J = 17.7, 1.5 Hz, CH=C$H_{(trans)}$), 5.23 (1H, dd, J = 11.1, 1.5 Hz, CH=C$H_{(cis)}$), 4.25 (1H, sextet, J = 6.0 Hz, C*H*CH_3), 3.77 (3H, s, CH_3OPh), 2.39 (2H, t, J = 7.0 Hz, CH_2CO), 1.87-1.59 (4H, m, CHCH_2CH_2), 1.25 (3H, d, J = 6.0 Hz, CH_3CH); δ_C (100 MHz; $CDCl_3$) 179.5 (C), 153.9 (C), 149.3 (C), 131.7 (ArCH), 129.1 (C), 116.3 (ArCH), 114.3 (=CH_2), 114.2 (=CH), 111.2 (ArCH), 75.4 (CH), 55.7 (CH_3), 35.9 (CH_2), 33.9 (CH_2), 20.8 (CH_2), 19.8 (CH_3); m/z [FAB^+] 265.0 (M^+, 56 %) [found 265.1437 $C_{15}H_{21}O_4$ expected 265.1440].

5-(4-Methoxy-2-vinylphenoxy)hexanoylamino-PEGA 116



Amino PEGA resin pre-swollen in methanol (2.5 g) was washed with dimethylformamide (2 x 15 mL), tetrahydrofuran (2 x 15 mL), dichloromethane (2 x 15 mL) and dried under vacuum to give dry amino PEGA resin (0.33 g) which was left 1 hour to swell in dimethylformamide (4 mL). In a reaction vessel, di-*iso*-propylcarbodiimide (0.11 mL, 0.69 mmol) and 1-hydroxybenzotriazole (0.09 g, 0.69 mmol) were added to a solution of 5-(2-form-yl-4-methoxyphenoxy)hexanoic acid **114** (0.18 g, 0.69 mmol) in dimethylformamide (2.5 mL). The reaction mixture was stirred for 15 minutes and then added to the pre-swollen resin in dimethylformamide. The reaction mixture was stirred for 22 hours by vertical rotation, and washed with sequential portions of dimethylformamide (7 x 15 mL) and dichloromethane (3 x 15 mL). A solution of triethylamine (0.65 mL, 4.6 mmol) and dimethylaminopyridine (48 mg, 0.39 mmol) in dichloromethane (3 mL) was added to the resin, followed by addition of acetic anhydride (0.40 g, 3.9 mmol) in the same solvent (1 mL). The resulting mixture was stirred for 24 hours by vertical rotation, and washed with sequential portions of dichloromethane (3 x 15 mL), dimethylformamide (3 x 15 mL), water (3 x 15 mL), dimethylformamide (3 x 15 mL), dichloromethane (3 x 15 mL) and diethyl ether (3 x 15 mL). The resin was then dried in a drying pistol to obtain the desired resin **116** (0.47 g). (A small portion of the resin was subjected to the Kaiser test, which was negative). ν_{max} cm^{-1} (film) 1715 ($C{=}O_{amide}$).

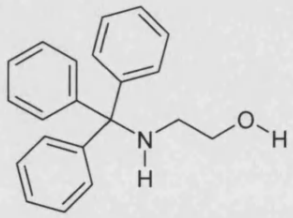
Second generation PEGA-supported initiator methoxy analogue 118



A sonicated solution of second generation Grubbs catalyst (14 mg, 16 μmol) in degassed 1,2-dichloroethane (1 mL) was added to a suspension of 5-(4-methoxy-2-vinylphenoxy)hexanoylamino-PEGA **116** (0.46 g, 0.16 mmol) in 1,2-dichloroethane (3 mL). The vessel was sealed to another plastic vessel (role of air-condenser) and heated to 40 °C for 4 hours, followed by washing with dichloromethane until the filtrate was clear. This entire operation was repeated five times. The new resin was finally dried under vacuum to afford the required compound **118** as green beads. ICP-AES: Ru ($mmol_{Ru}/g_{initiator}$) = 0.106.

7.3 Water soluble imidazolylidene ligand

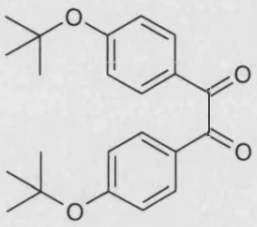
2-Tritylaminoethanol 121[107]



A solution of triphenylmethyl chloride **123** (4.6 g, 17 mmol) in chloroform (10 mL) was added to ethanolamine **122** (1.0 mL, 17 mmol) and triethylamine (4.6 mL, 33 mmol) in chloroform (20 mL). The reaction mixture was stirred at room temperature for 24 hours and was washed successively with 10 % aqueous citric acid (20 mL) and water (20 mL). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to leave a yellow oil, which was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 50:50) as eluent to give compound **121** (2.9 g, 58 %) as a colourless oil. R_f 0.22 (1:2 diethyl ether: hexane); ν_{max} cm^{-1} (film) 3400-3100 (O-H/N-H), 3100-3000 (=CH), 3000-2850 (C-H),

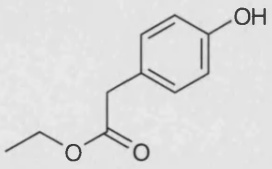
1596 (N-H), 1488 (C=C), 1448 (-CH), 1030 (CH_2-OH); δ_H (400 MHz; $CDCl_3$) 7.51-7.18 (15H, m, Ar*H*), 3.70 (2H, t, *J* = 5.3 Hz, CH_2OH), 2.36 (2H, t, *J* = 5.3 Hz, CH_2NH), 2.00 (2H, 2 x bs, N*H* and O*H*); δ_C (100 MHz; $CDCl_3$) 145.9 (3 x C), 128.8 (6 x ArCH), 128.1 (6 x ArCH), 126.6 (3 x ArCH), 70.9 (C), 63.0 (CH_2), 46.0 (CH_2).

Attempt preparation of *bis*(4-*tert*-butoxyphenyl)ethanedione 125[109]



In a pressure tube 4,4'-dibromobenzil **120** (0.10 g, 0.28 mmol) was dissolved in hot toluene (1 mL at 100°C). $Pd(dba)_2$ (12 mg, 13 μmol), bis(diphenylphosphinyl)ferrocene (5.7 mg, 10 μmol) and potassium *tert*-butoxide (81 mg, 0.72 mmol) were added and the reaction mixture was stirred for 20 hours at 100 °C. The resulting black mixture was cooled, filtered through Celite and concentrated to afford mono-(4-*tert*-butoxy-phenyl)-ethanedione **125** as shown by the NMR spectra. δ_H (400 MHz; $CDCl_3$) 7.48-7.27 (8H, m, Ar*H*), 1.46 (9H, s, 3xCH_3).

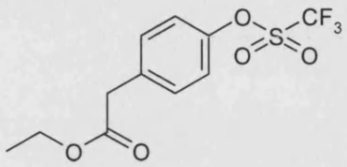
Ethyl 4'-hydroxyphenylacetate 127[147,148]



A solution of 4'-hydroxyphenylacetic acid **126** (5.0 g, 33 mmol) and sulfuric acid (2.6 mL, 50 mmol) in ethanol (50 mL) was heated at reflux for 5h and the reaction mixture was allowed to cooled to room temperature. After addition of water (30 mL) and dichloromethane (30 mL), the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic fractions were washed with brine (20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give **127** as a colourless oil (5.6 g, 96 %). R_f 0.42 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3400-3100 (OH), 3100-3000 (ArH), 3000-2850 (C-H), 1711 (C=O), 1517 (C-H), 1371 (CH_3), 1224 (C-O); δ_H (270 MHz; $CDCl_3$) 7.07 (2H, d, *J* = 8.4 Hz, Ar$H_{(3)}$), 6.70 (2H, d, *J*

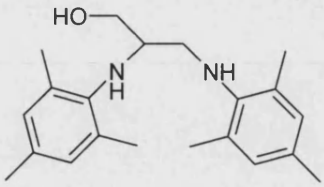
= 8.4 Hz, Ar$H_{(2)}$), 6.18 (1H, bs, O*H*), 4.15 (2H, q, *J* = 7.2 Hz, CH_2CH$_3$), 3.53 (2H, s, CH_2CO), 1.25 (3H, t, *J* = 7.2 Hz, CH_3CH$_2$); δ_C (100 MHz; $CDCl_3$) 173.0 (C), 155.1 (C), 130.4 (2 x ArCH), 125.7 (C), 115.6 (2 x ArCH), 61.2 (CH_2), 40.6 (CH_2), 14.2 (CH_3); m/z [EI^+] 181.1 (M^+, 85 %) [found 181.0815 $C_{10}H_{13}O_3$ expected 181.0865].

Ethyl 4'-trifluoromethanesulfonyloxyphenylacetate 128



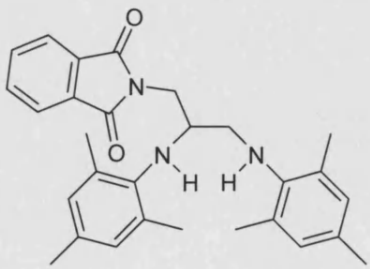
A solution of ethyl 4'-hydroxyphenylacetate **127** (1.0 g, 5.6 mmol) and pyridine (2.3 mL, 28 mmol) in dichloromethane (10 mL) was cooled to 0 °C, in an ice bath. Trifluoromethanesulfonic anhydride (1.1 mL, 6.7 mmol) was added slowly to the reaction mixture, which was stirred for 1 h, then diluted with water (20 mL). The reaction mixture was partitioned between dichloromethane (30 mL) and sodium hydroxide (0.5 M, 15 mL, 15 mmol). The organic layer was washed successively with water (20 mL), hydrochloric acid (0.1 M, 2 x 25 mL), water (20 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to afford **128** as a yellow oil (1.6 g, 93 %). R_f 0.77 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1737 (C=O), 1424 (C-H), 1370 (CH_3), 1216 (C-O); δ_H (270 MHz; $CDCl_3$) 7.36 (2H, d, *J* = 8.4 Hz, Ar$H_{(3)}$), 7.22 (2H, d, *J* = 8.4 Hz, Ar$H_{(2)}$), 4.15 (2H, q, *J* = 7.2 Hz, CH_2CH$_3$), 3.62 (2H, s, CH_2CO), 1.25 (3H, t, *J* = 7.2 Hz, CH_3CH$_2$); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 148.7 (C), 134.7 (C), 131.2 (2 x ArCH), 121.4 (2 x ArCH), 121.2 (C), 61.2 (CH_2), 40.6 (CH_2), 14.2 (CH_3); m/z [FAB^+] 313.0 (M^++H, 100 %) [found 313.0358 $C_{11}H_{12}O_5SF_3$ expected 313.0357].

2,3-*Bis*-(2,4,6-trimethylphenylamino)propan-1-ol 136[114]



2,3-Dibromopropanol **125** (2.4 mL, 23 mmol) and 2,4,6-trimethylaniline **84** (9.0 mL, 64 mmol) were stirred at 120 °C for 24 hours. To the resulting brown precipitate was added dichloromethane (30mL) and sodium hydroxide (15 % aqueous, ~25 mL) and the mixture was stirred until all solid was dissolved. The organic fraction was separated, washed with water (20 mL), dried over magnesium sulfate and concentrated to give a dark brown oil which was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 50:50) as eluent affording **136** as a white solid (6.0 g, 79 %). R_f 0.33 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (KBr disc) 3416 (OH/NH), 3100-3000 (ArH), 3000-2850 (C-H), 1617 (N-H), 1484 (C=C arom), 1445 (C-H), 1373 (CH_3), 1058 (C-O (CH_2OH)), 850 (C-H arom); δ_H (400 MHz; $CDCl_3$) 6.83 (2H, s, Ar*H*), 6.81 (2H, s, Ar*H*), 3.97 (1H, dd, *J* = 10.9, 3.0 Hz, CH_aH$_b$OH), 3.84 (1H, dd, *J* = 10.9, 3.0 Hz, CH$_a$*H*$_b$OH), 3.62 (2H, bs, 2 x N*H*), 3.39 (1H, m, C*H*), 3.23 (1H, dd, *J* = 11.9, 5.2 Hz, CH_aH$_b$NH), 2.99 (1H, dd, *J* = 11.9, 3.7 Hz, CH$_a$*H*$_b$NH), 2.29 (6H, s, 2 x CH_{3ortho}), 2.24 (3H, s, CH_{3para}), 2.22 (3H, s, CH_{3para}), 2.17 (6H, s, 2 x CH_{3ortho}); δ_C (100 MHz; $CDCl_3$) 142.5 (C), 141.9 (C), 132.6 (C), 131.0 (C), 130.7 (2 x C), 129.9 (2 x ArCH), 129.6 (2 x ArCH), 128.8 (2 x C), 66.2 (CH_2), 56.9 (CH), 52.4 (CH_2), 20.6 (CH_3), 20.5 (CH_3), 19.0 (2 x CH_3), 17.8 (2 x CH_3); m/z [FAB^+] 327.3 (M^++H, 60 %).

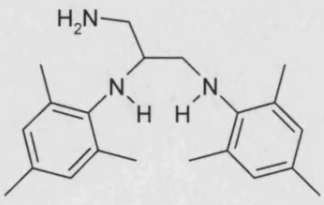
2,3-*Bis*(2,4,6-trimethylphenylamino)-1-phthalamidopropane 140



Carbon tetrabromide (0.61 g, 1.8 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a solution of 2,3-*bis*-(2,4,6-trimethyl-phenylamino)propan-1-ol **136** (0.50 g, 1.5 mmol), triphenylphosphine (0.96 g, 3.7 mmol) and pyridine (0.15 mL, 1.8 mmol) in

dry tetrahydrofuran (20 mL) at 0 °C. The reaction mixture was stirred for 3 hours at room temperature afterwhich it was concentrated under reduced pressure. Purification by flash chromatography using a gradient of 1:4 diethyl ether:hexane as eluent afforded a mixture of compounds (**138** and **139**) which was dissolved in dimethylformamide (5mL). Potassium phthalimide was added and the reaction mixture was stirred for 24 hours at 80 °C, concentrated under vacuum and dichloromethane (10 mL) and water (10 mL) were added. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the **140** (0.29 g, 86 %) as a yellow solid. R_f 0.46 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 320 (N-H), 3100-3000 (ArH), 3000-2850 (C-H), 1752 (C=O), 1735 (C=O), 1483 (C=C arom), 1376 (CH_3), 853 (C-H arom); δ_H (400 MHz; $CDCl_3$) 7.92 (1H, bs, N*H*), 7.91-7.78 (4H, m, Ar$H_{phthalimide}$), 6.85 (2H, d, J = 0.5 Hz, Ar*H*(NHCH)), 6.80 (2H, d, J = 0.5 Hz, Ar*H*($NHCH_2$)), 3.65 (1H, dd, J = 12.8, 2.8 Hz, CH_aH_bNH), 3.36 (1H, bs, N*H*), 3.16 (1H, dd, J = 12.8, 6.2 Hz, CH_aH_bNH), 2.50 (1H, dd, J = 3.3, 0.8 Hz, $CH_aH_bN_{phthalimide}$), 2.43 (1H, ddt, J = 6.2, 3.3, 2.8 Hz, C*H*), 2.35 (6H, s, 2 x CH_{3ortho}PhNHCH), 2.32 (6H, s, 2 x $CH_{3ortho}PhNHCH_2$), 2.27 (3H, s, CH_{3para}PhNHCH), 2.25 (3H, s, $CH_{3para}PhNHCH_2$), 2.02 (1H, dd, J = 6.2, 0.8 Hz, $CH_aH_bN_{phthalimide}$); δ_C (100 MHz; $CDCl_3$) 167.8 (2 x C_{amide}), 148.1 (C_{mes}), 143.0 (C_{mes}), 134.3 (2 x $ArCH_{phthalimide}$), 132.6 (2 x $C_{phthalimide}$), 131.4 (C_{mes}), 131.1 (C_{mes}), 129.7 (C_{mes}), 129.6 (2 x $ArCH_{mes}$), 129.4 (2 x $ArCH_{mes}$), 128.9 (C_{mes}), 123.6 (2 x $ArCH_{phthalimide}$), 49.2 (CH_2), 40.4 (CH), 34.9 (CH_2), 20.8 (CH_3), 20.7 (CH_3), 19.3 (2 x CH_3), 18.6 (2 x CH_3); m/z [FAB^+] 456.2 (M^++H, 50 %) [found 456.2640 $C_{29}H_{34}N_3O_2$ expected 456.2651].

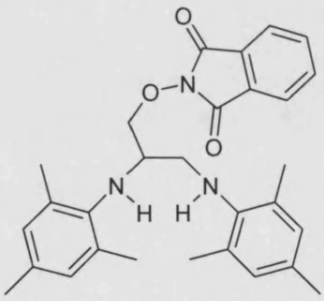
N,N'-Bis(2,4,6-trimethylphenyl)propane-1,2,3-triamine 142



2,3-*Bis*(2,4,6-trimethylphenylamino)-1-phthalamidopropane **140** (2.1 g, 4.7 mmol) and hydrazine hydrate (0.46 mL, 15 mmol) in ethanol (10 mL) were heated under reflux for two hours and poured into a solution of 3 % aqueous sodium carbonate. The mixture was extracted with dichloromethane (3 x 20 mL), washed with water (2 x 15 mL), dried with

anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using a gradient of diethyl ether:hexane (0:100 → 50:50) as eluent to give *N,N'*-b*is*(2,4,6-trimethylphenyl)propane-1,2,3-triamine **142** as a clear colourless oil (1.5 g, 98 %). R_f 0.37 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3350 (N-H), 3100-3000 (=CH), 3000-2850 (C-H), 1646 (C=C), 1593 (N-H), 1392 (CH_3); δ_H (400 MHz; $CDCl_3$) 6.82 (2H, s, Ar*H*(NHCH)), 6.76 (2H, s, Ar*H*(NHCH$_2$)), 3.60 (1H, dd, *J* = 12.9, 2.7 Hz, C*H*$_a$H$_b$NH), 3.11 (1H, dd, *J* = 12.9, 6.2 Hz, CH$_a$*H*$_b$NH), 2.45 (1H, dd, *J* = 3.5, 0.7 Hz, C*H*$_a$H$_b$NH$_2$), 2.38 (1H, ddt, *J* = 6.2, 3.5, 2.7 Hz, C*H*), 2.30 (6H, s, 2 x C*H*$_{3ortho}$(PhNHCH)), 2.27 (6H, s, 2 x C*H*$_{3ortho}$(PhNHCH$_2$)), 2.22 (3H, s, C*H*$_{3para}$(PhNHCH)), 2.21 (3H, s, C*H*$_{3para}$(PhNHCH$_2$)), 1.97 (1H, dd, *J* = 6.2, 0.7 Hz, CH$_a$*H*$_b$NH$_2$); δ_C (100 MHz; $CDCl_3$) 148.3 (C), 143.2 (C), 131.4 (C), 131.1 (C), 129.7 (2 x C), 129.6 (ArCH), 129.5 (ArCH), 128.9 (2 x C), 49.1 (CH_2), 40.2 (CH), 34.7 (CH_2), 20.6 (CH_{3para}), 20.4 (CH_{3para}), 19.1 (CH_{3ortho}), 18.4 (CH_3).

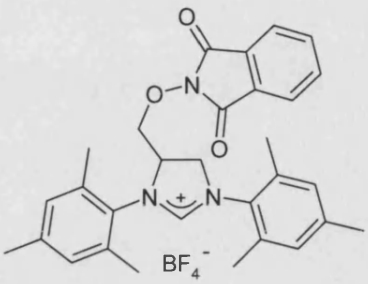
2,3-*Bis*(2,4,6-trimethylphenylamino)propoxyphthalimide 144[115]



Diethyl azodicarboxylate (0.56 mL, 3.4 mmol) was added dropwise to a solution of 2,3-*bis*-(2,4,6-trimethylphenylamino)propan-1-ol **136** (1.0 g, 3.1 mmol), *N*-hydroxy-phthalimide (0.50 g, 3.1 mmol) and triphenylphosphine (0.80 g, 3.1 mmol) in anhydrous tetrahydrofuran (15 mL) at room temperature. The reaction mixture was stirred for 24 hours under nitrogen, concentrated under reduced pressure and purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 20:80) as eluent to give 2,3-*bis*-(2,4,6-trimethyl-phenylamino)propan-1-oxyphthalimide **144** (0.58 g, 40 %) as a yellow solid. mp 145 °C; R_f 0.50 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3368 (N-H), 3100-3000 (ArH), 3000-2850 (C-H), 1732(C=O), 1372 (CH_3), 1188 (C-O); δ_H (400 MHz; $CDCl_3$) 7.91-7.77 (4H, m, Ar$H_{phthalimide}$), 6.87 (2H, s, Ar*H*(NHCH)), 6.86 (2H, s, Ar*H*(NHCH$_2$)), 4.38 (2H, d, *J* = 3.6 Hz, OC*H*$_2$CH), 3.83-3.63 (3H, m, C*H* and 2 x N*H*), 3.53 (1H, dd, *J* = 12.8, 6.8 Hz, NHC*H*$_a$H$_b$CH), 3.19 (1H, dd, *J* = 12.8, 5.9 Hz,

$NHCH_aH_bCH$), 2.37 (6H, s, 2 x $CH_{3ortho}(NHCH)$), 2.35 (6H, s, 2 x $CH_{3ortho}(NHCH_2)$), 2.27 (3H, s, $CH_{3para}(NHCH)$), 2.26 (3H, s, $CH_{3para}(NHCH_2)$); δ_C (100 MHz; $CDCl_3$) 163.3 (2 x C_{imide}), 143.6 (C_{mes}), 141.0 (C_{mes}), 134.6 (2 x $ArCH_{phthalimide}$), 134.4 (2 x $C_{phthalimide}$), 131.5 (C_{mes}), 131.2 (C_{mes}), 130.4 (2 x C_{mes}), 129.7 (2 x $ArCH_{mes}$), 129.4 (2 x $ArCH_{mes}$), 128.9 (2 x C_{mes}), 123.6 (2 x $ArCH_{phthalimide}$), 78.3 (CH_2), 56.1 (CH), 49.5 (CH_2), 20.5 (2 x CH_3), 18.8 (2 x CH_3), 18.3 (2 x CH_3); m/z [FAB^+] 472.2 (M^++H, 36 %) [found 472.25812 $C_{29}H_{34}N_3O_3$ expected 472.2600].

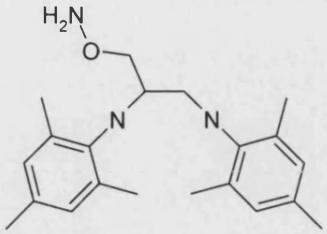
1,3-*Bis*(2,4,6-trimethylphenyl)-4-phthalimidooxy-4,5-dihydroimidazolium tetrafluoroborate 145[90]



Ammonium tetrafluoroborate (22 mg, 0.21 mmol) was added to 2,3-*bis*(2,4,6-trimethylphenylamino)propoxyphthalimide **144** (0.10 g, 0.21 mmol) followed by triethyl orthoformate (0.04 mL, 0.21 mmol). The reaction mixture was heated at reflux for 3 hours then cooled to room temperature. The resulting precipitate was collected by filtration and recrystallised from hot anhydrous ethanol. The resulting white crystals of product **145** were recovered by vacuum filtration, washed with hexane, and dried under high vacuum (62 mg, 89 %). mp 266 °C; R_f 0.57 (9:1 dichloromethane:methanol); ν_{max} cm^{-1} (disc) 3100-3000 (=CH), 3000-2850 (C-H), 1736 (NC=O), 1629 (C=N), 1484 (-CH), 1383 (CH_3), 1266 (C-O); δ_H (400 MHz; DMSO-d_6) 9.17 (1H, s, NC*H*N), 7.89 (4H, s, $ArH_{phthalimide}$), 7.16 (1H, s, ArH_{mes}), 7.12 (3H, s, 3 x ArH_{mes}), 5.30 (1H, m, CH_2CHCH_2), 4.83 (1H, t, J = 11.9 Hz, CH_aH_bO), 4.76 (1H, dd, J = 11.9, 7.6 Hz, CH_aH_bO), 4.45 (1H, dd, J = 11.6, 2.6 Hz, CH_aH_bNH), 4.32 (1H, dd, J = 11.6, 3.1 Hz, CH_aH_bNH), 2.49 (3H, s, CH_{3ortho}), 2.41 (3H, s, CH_{3ortho}), 2.38 (3H, s, CH_{3para}), 2.36 (3H, s, CH_{3para}), 2.32 (3H, s, CH_{3ortho}), 2.31 (3H, s, CH_{3ortho}); δ_C (100 MHz; DMSO-d_6) 168.4 (CH), 163.3 (2 x C_{imide}), 140.4 (C_{mes}), 140.2 (C_{mes}), 136.8 (C_{mes}), 136.0 (2 x C_{mes}), 135.4 (2 x $ArCH_{phthalimide}$), 131.2 ($C_{phthalimide}$), 130.4 ($ArCH_{mes}$), 130.3 ($ArCH_{mes}$), 130.0 (2 x $ArCH_{mes}$), 129.0 (2 x C_{mes}), 128.8 (C_{mes}), 123.9 (2 x $ArCH_{phthalimide}$), 75.3 (CH_2), 62.1

(CH), 52.5 (CH_2), 21.0 (2 x CH_3), 18.3 (CH_3), 18.1 (CH_3), 17.7 (2 x CH_3); m/z [FAB^+] 482.1 (M^++H, 100 %) [found 482.24467 $C_{30}H_{32}N_3O_3$ expected 482.2444].

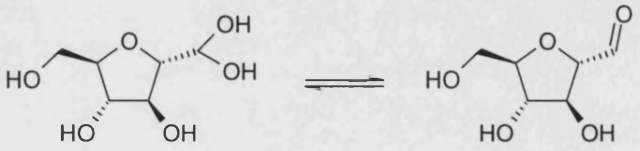
2,3-*Bis*(2,4,6-trimethylphenylamino)propoxyamine 147



2,3-*Bis*(2,4,6-trimethylphenylamino)propoxyphthalimide **144** (0.20 g, 0.42 mmol) and hydrazine hydrate (0.05 mL, 1.4 mmol) in ethanol (5 mL) were heated under reflux for two hours and poured into a solution of 3 % aqueous sodium carbonate. The reaction mixture was extracted with dichloromethane (3 x 10 mL), washed with water (10 mL), dried with anhydrous magnesium sulfate and filtered to give 2,3-*bis*(2,4,6-trimethylphenylamino)propoxyamine **147** (0.13 g, 92 %). R_f 0.29 (1:1 diethyl ether:hexane); δ_H (400 MHz; $CDCl_3$) 6.91 (4H, s, Ar*H*), 4.38 (2H, tt, *J* = 10.0, 4.0 Hz, OCH_2CH), 3.68 (1H, m, C*H*), 3.35 (1H, dd, *J* = 12.0, 6.0 Hz, $NHCH_aH_bCH$), 3.04 (1H, dd, *J* = 12.0, 6.5 Hz, $NHCH_aH_bCH$), 2.38 (6H, s, 2 x CH_{3ortho}(NHCH)), 2.35 (6H, s, 2 x $CH_{3ortho}(NHCH_2)$), 2.32 (6H, s, 2 x CH_{3para}); δ_C (100 MHz; $CDCl_3$) 143.7 (C), 141.8 (C), 131.3 (C), 131.0 (C), 129.8 (2 x C), 129.7 (2 x ArCH), 129.5 (2 x ArCH), 129.2 (2 x C), 76.7 (CH_2), 56.4 (CH), 50.7 (CH_2), 20.7 (CH_3), 20.6 (CH_3), 19.0 (2 x CH_3), 18.4 (2 x CH_3); m/z [FAB^+] 342.2 (M^++H, 56 %) [found 342.25523 $C_{21}H_{32}N_3O_1$ expected 342.2545].

7.4 Synthesis of a library of fructose transport inhibitors

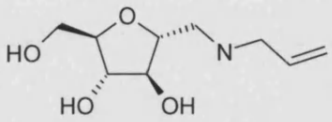
2,5-Anhydro-*D*-mannose 152[121]



A solution of 2-amino-2-deoxy-*D*-glucose hydrochloride **153** (4.2 g, 20 mmol) in water (100 mL) at mutarotational equilibrium (~5 h at 25 °C) was cooled to 0 °C. Sodium

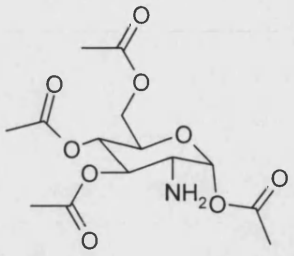
nitrite (3.4 g, 50 mmol) was added, followed by cation exchange resin (Amberlite IR-120, acid) in portions, the temperature being maintained at 0-5 °C during the addition. The mixture was stirred for 4 h at 0 °C then the resin was filtered and the filtrate was neutralised by addition of an anion-exchange resin (Dowex 1 x 8-50, basic). The solution was filtered and concentrated to give 2,5-anhydro-*D*-mannose **152** as a yellow-white solid (2.8 g, 80 %). R_f 0.40 (4:1 dichloromethane:methanol); ν_{max} cm^{-1} (disc) 3100-3400 (O-H), 3000-2850 (C-H), 1636 (C=O), 1270 (C-O), 1053 (C-O); δ_H (270 MHz; D_2O) 8.46 (0.4H, s, $C_{(1)}HO$), 5.10 (0.6H, d, J = 5.2 Hz, $C_{(1)}H(OH)_2$), 4.19 (1H, t, J = 6.0 Hz, $C_{(3)}H$), 4.07 (1H, t, J = 6.0 Hz, $C_{(4)}H$), 3.93 (1H, m, $C_{(2)}H$), 3.82-3.66 (3H, m, $C_{(5)}H$ and $C_{(6)}H_2$); δ_C (100 MHz; D_2O) 192.7 ($C_{(1)}HO$), 89.8 ($C_{(1)}H(OH)_2$), 84.4 ($C_{(2)}H$), 83.1 ($C_{(5)}H$), 77.6 ($C_{(3)}H$), 76.7 ($C_{(4)}H$), 61.1 ($C_{(6)}H_2$); m/z [FAB^+] 163.1 (M^++H, 26 %).

1-Prop-2-enylamino-1-*deoxy*-2,5-anhydro-*D*-mannitol 150[121]



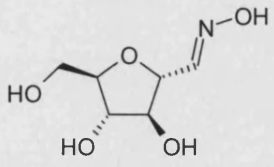
Sodium cyanoborohydride (0.23 g, 3.6 mmol) was added to a solution of 2,5-anhydro-*D*-mannose **152** (1.0 g, 5.6 mmol) in methanol (15 mL). The reaction mixture was stirred for 18 hours then flushed through acidic Dowex 50WX2-100 and rinsed with methanol. After changing the collecting flask, the resin was washed with methanolic ammonia (3 x 10 mL) and the resulting solution was concentrated to give a yellow oil. Purification by flash chromatography on silica using a gradient of methanol:dichloromethane (0:100 → 10:90) as eluent afforded **150** as a light oil (0.38 g, 30 %). ν_{max} cm^{-1} (film) 3400-3100 (O-H/N-H), 3000-2850 (C-H), 1641 (C=C), 1058 (C-O), 948 (-CH=CH_2); δ_H (270 MHz; Methanol-d_3) 5.96 (1H, ddt, J = 17.2, 10.3, 6.6 Hz, CH=CH_2), 5.56 (1H, d, J = 17.2 Hz, CH=$CH_{(trans)}$), 5.50 (1H, d, J = 10.3 Hz, CH=$CH_{(cis)}$), 4.12 (1H, q, J = 5.9 Hz, $C_{(2)}H$), 4.03 (1H, t, J = 4.7 Hz, $C_{(4)}H$), 3.96 (1H, m, $C_{(5)}H$), 3.91 (1H, t, J = 4.7 Hz, $C_{(3)}H$), 3.78-3.62 (4H, m, CH_2CH= and $C_{(6)}H_2$), 3.58 (2H, d, J = 6.6 Hz, CH_2NH); δ_C (100 MHz; $CDCl_3$) 127.2 (CH=), 124.2 (CH_2=), 83.5 ($C_{(5)}H$), 78.7 ($C_{(2)}H$), 78.4 ($C_{(3)}H$), 76.7 ($C_{(4)}H$), 61.4 ($C_{(6)}H_2$), 50.0 (CH_2), 48.5 ($C_{(1)}H_2$); m/z [FAB^+] 204.1 (M^++H, 100 %) [found 204.1233 $C_9H_{18}NO_4$ expected 204.1236].

1,3,4,6-Tetra-acetoxy-*D*-glucosamine 157



Acetic anhydride (25 mL, 0.26 mol) was added to a solution of *D*-glucosamine hydrochloride **153** (7.0 g, 32 mmol), in pyridine (26 mL, 0.32 mol) and the reaction mixture was stirred for 16 hours at room temperature. After addition of water (30 mL) and dichloromethane (30 mL), the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic fractions were washed with brine (20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give **157** as a white solid (11 g, 90 %). R_f 0.67 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3400-3100 (N-H), 3000-2850 (C-H), 1742 (C=O), 1383 (CH_3), 1040 (C-O), 943 (-$CH{=}CH_2$); δ_H (400 MHz; $CDCl_3$) 6.07 (1H, d, J = 3.7 Hz, $C_{(1)}H$), 5.30 (1H, dd, J = 10.9, 9.4 Hz, $C_{(3)}H$), 5.10 (1H, t, J = 9.4 Hz, $C_{(4)}H$), 4.39 (1H, dd, J = 10.9, 3.7 Hz, $C_{(2)}H$), 4.29 (1H, dd, J = 12.5, 4.1 Hz, $C_{(6a)}H$), 4.14 (1H, ddd, J = 10.1, 4.1, 2.3 Hz, $C_{(5)}H$), 4.05 (1H, dd, J = 12.5, 2.3 Hz, $C_{(6b)}H$), 2.06 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.92 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 171.0 (C), 170.6 (C), 169.9 (C), 169.4 (C), 90.4 ($C_{(1)}H$), 70.7 ($C_{(5)}H$), 69.9 ($C_{(3)}H$), 68.7 ($C_{(4)}H$), 61.8 ($C_{(6)}H$), 50.9 ($C_{(2)}H$), 21.3 (CH_3), 19.7 (CH_3), 19.6 (2 x CH_3); m/z [FAB^-] 346.3 (M^+-H, 31 %).

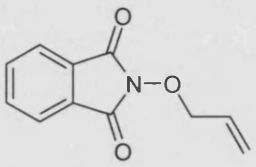
2,5-Anhydro-1-oxime *D*-mannose 161[121]



Hydroxylamine hydrochloride (0.58 g, 8.3 mmol) and sodium acetate (0.91 g, 11 mmol) were successively added to a solution of 2,5-anhydro-*D*-mannose **152** (1.0 g, 5.6 mmol) in methanol (40 mL). The solution was stirred for 18 hours at room temperature and the methanol was then removed under reduced pressure with the resulting syrup being dissolved in absolute ethanol to precipitate the salts. After filtration, complete removal of

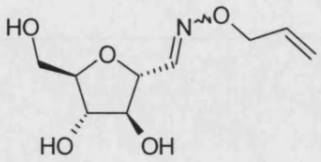
solvent gave the oxime **161** (0.68 g, 69 %; two isomers observed (4:1 A:B)). R_f 0.58 (4:1 dichloromethane:methanol); **isomer A**: δ_H (400 MHz; DMSO-d_6) 7.30 (1H, d, J = 7.7 Hz, C*H*N), 4.13 (1H, dd, J = 7.7, 5.3 Hz, $C_{(2)}H$), 3.88 (1H, dd, J = 5.3, 5.1 Hz, $C_{(3)}H$), 3.85 (1H, t, J = 5.1 Hz, $C_{(4)}H$), 3.71 (1H, dt, J = 5.1, 4.2 Hz, $C_{(5)}H$), 3.50 (1H, dt, J = 11.5, 4.2 Hz, $C_{(6)}H_aH_b$), 3.44 (1H, dt, J = 11.5, 5.1 Hz, $C_{(6)}H_aH_b$); δ_C (100 MHz; DMSO-d_6) 149.5 ($C_{(1)}H$), 85.0 ($C_{(5)}H$), 81.2 ($C_{(2)}H$), 80.1 ($C_{(3)}H$), 77.3 ($C_{(4)}H$), 62.0 ($C_{(6)}H_2$); **isomer B**: δ_H (400 MHz; DMSO-d_6) 6.68 (1H, d, J = 5.6 Hz, C*H*N), 4.83 (1H, dd, J = 5.6, 2.6 Hz, $C_{(2)}H$), 3.88 (1H, dd, J = 5.3, 5.1 Hz, $C_{(3)}H$), 3.85 (1H, t, J = 5.1 Hz, $C_{(4)}H$), 3.71 (1H, dt, J = 5.1, 4.2 Hz, $C_{(5)}H$), 3.50 (1H, dt, J = 11.5, 4.2 Hz, $C_{(6)}H_aH_b$), 3.44 (1H, dt, J = 11.5, 5.1 Hz, $C_{(6)}H_aH_b$); δ_C (100 MHz; DMSO-d_6) 151.6 ($C_{(1)}H$), 87.2 ($C_{(5)}H$), 80.7 ($C_{(3)}H$), 79.4 ($C_{(2)}H$), 77.9 ($C_{(4)}H$), 62.3 ($C_{(6)}H_2$); m/z [FAB^+] 176.0 (M^+-H, 100 %).

_N_-(Prop-2-enyloxy)phthalimide 163[125]



N-Hydroxyphthalimide **164** (9.0 g, 55 mmol) was added dropwise to a solution of sodium hydride (4.4 g, 0.11 mol) in dry tetrahydrofuran (100 mL) at 0 °C (Caution: exothermic). The mixture was stirred for 15 minutes and allyl bromide (8.0 g, 66 mmol) was added dropwise and the solution was stirred for 17 hours. The reaction mixture was quenched with water and acidified with hydrochloric acid (1 M). The reaction mixture was partitioned between diethyl ether (50 mL) and water (50 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organics were washed with brine (50 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of methanol:dichloromethane (0:100 → 10:90) as eluent gave *N*-(prop-2-enyloxy)phthalimide **163** as a white solid (6.2 g, 55 %). m.p. 52 °C (lit. m.p. 56-57 °C)[125] ; R_f 0.63 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (disc) 3100-3000 (=C-H), 3000-2850 (C-H), 1639 (C=O), 1185 (C-O), 992 (-CH=CH_2); δ_H (270 MHz; $CDCl_3$) 7.85-7.70 (4H, m, Ar*H*), 6.11 (1H, ddt, J = 17.0, 10.1, 6.7 Hz, C*H*=CH_2), 5.34 (1H, dd, J = 17.0, 1.0 Hz, CH=C$H_{(trans)}$), 5.33 (1H, d, J = 10.1 Hz, CH=C$H_{(cis)}$), 4.69 (2H, d, J = 6.7 Hz, NCH_2); δ_C (100 MHz; $CDCl_3$) 163.4 (2 x C), 134.6 (2 x ArCH), 131.4 (2 x ArCH), 129.0 (2 x C), 123.7 (CH=), 122.9 (CH_2=), 79.2 (CH_2); m/z [FAB^+] 204.0 (M^++H, 100 %).

2,5-Anhydro-1-(prop-2-enyl)oxime-*D*-mannitol 167

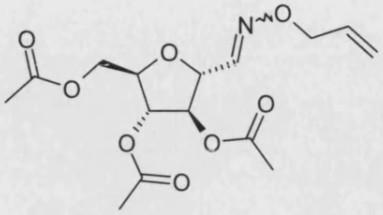


N-(Prop-2-enyloxy)phthalimide **163** (2.0 g, 9.8 mmol), hydrazine hydrate (1.0 mL, 32 mmol) in ethanol (30 mL) were heated under reflux (~120 °C) for two hours and poured into a solution of 3 % aqueous sodium carbonate which was extracted with dichloromethane, washed with water, dried and filtered. To this organic phase was added hydrochloric acid in methanol (4 M, 10 mL, 40 mmol) to give *O*-prop-2-enylhydroxylamine hydrochloric salt **166** (0.86 g, 80 %).

A solution of *O*-prop-2-enylhydroxylamine hydrochloric salt (0.38 g, 3.5 mmol) in dimethylformamide (10 mL) was added *via* a cannula to a solution of 2,5-anhydro-*D*-mannose (0.38 g, 2.1 mmol) in dimethylformamide (20 mL). Pyridine (0.32 mL, 4.0 mmol) was then added and the reaction mixture was stirred for 20 h at room temperature. After concentration, the solid residue was then purified by flash chromatography on silica using a gradient of methanol:dichloromethane (0:100 → 10:90) as eluent affording **167** as a light yellow oil (0.20 g, 41 %; two isomers observed (4:1 A:B)). R_f 0.51 (1:9 methanol:dichloromethane); ν_{max} cm^{-1} (film) 3400-3100 (O-H/N-H), 3000-2850 (C-H), 1646 (C=C), 1021 (C-O), 929 (-CH=CH_2); **isomer A**: δ_H (400 MHz; $CDCl_3$) 7.44 (1H, d, *J* = 7.4 Hz, C*H*N), 5.91-6.07 (1H, m, C*H*=CH_2), 5.27 (1H, ddq, *J* = 17.2, 7.8, 1.6 Hz, CH=C$H_{(trans)}$), 5.15-5.20 (1H, m, CH=C$H_{(cis)}$), 4.52 (2H, dt, *J* = 5.4, 1.6 Hz, CH_2), 4.32-4.28 (1H, ddd, *J* = 7.4, 5.3, 2.3 Hz, $C_{(2)}H$), 4.08-4.00 (2H, m, $C_{(3)}H$ and $C_{(4)}H$), 3.88 (1H, dt, *J* = 5.3, 3.7 Hz, $C_{(5)}H$), 3.70 (1H, dd, *J* = 11.7, 3.7 Hz, $C_{(6a)}H$), 3.64 (1H, dt, *J* = 11.7, 5.3 Hz, $C_{(6b)}H$); δ_C (100 MHz; $CDCl_3$) 149.3 ($C_{(1)}$H), 134.3 ($CH_{(cis)}$=), 134.2 ($CH_{(trans)}$=), 116.6 ($CH_{2(trans)}$=), 116.5 ($CH_{2(cis)}$=), 84.9 ($C_{(2)}$H), 81.3 ($C_{(5)}$H), 80.2 (CH), 77.4 (CH), 75.0 ($CH_{2(cis)}$), 74.7 ($CH_{2(trans)}$), 62.0 ($C_{(6)}H_2$); **isomer B**: δ_H (400 MHz; $CDCl_3$) 6.81 (1H, d, *J* = 7.4 Hz, C*H*N), 5.91-6.07 (1H, m, C*H*=CH_2), 5.27 (1H, ddq, *J* = 17.2, 7.8, 1.6 Hz, CH=C$H_{(trans)}$), 5.15-5.20 (1H, m, CH=C$H_{(cis)}$), 4.97 (1H, dd, *J* = 5.3, 2.3 Hz, $C_{(2)}H$), 4.56 (2H, dq, *J* = 5.4, 1.6 Hz, CH_2), 4.08-4.00 (2H, m, $C_{(3)}H$ and $C_{(4)}H$), 3.88 (1H, dt, *J* = 5.3, 3.7 Hz, $C_{(5)}H$), 3.70 (1H, dd, *J* = 11.7, 3.7 Hz, $C_{(6a)}H$), 3.64 (1H, dt, *J* = 11.7, 5.3 Hz, $C_{(6b)}H$); δ_C (100 MHz; $CDCl_3$) 152.1 ($C_{(1)}$H), 134.3 ($CH_{(cis)}$=), 134.2 ($CH_{(trans)}$=), 116.6 ($CH_{2(trans)}$=), 116.5 ($CH_{2(cis)}$=), 87.1 ($C_{(2)}$H) 81.0 ($C_{(5)}$H), 80.5 (CH), 77.9 (CH), 75.0

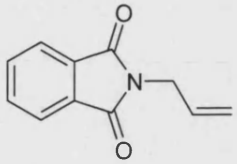
($CH_{2(cis)}$), 74.7 ($CH_{2(trans)}$), 62.3 ($C_{(6)}H_2$); m/z [FAB^+] 218.2 (M^++H, 100 %) [found 218.1023 $C_9H_{16}NO_5$ expected 218.1028].

3,4,6-Triacetoxy-2,5-anhydro-1-(prop-2-enyl)oxime-*D*-mannitol 170



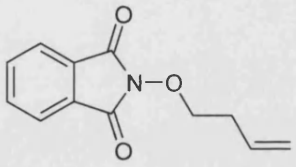
Acetic anhydride (2.1 mL, 22 mmol) was added to a solution of 2,5-anhydro-1-(prop-2-enyl)oxime-*D*-mannitol **167** (0.80 g, 3.68 mmol) in pyridine (9.0 mL, 0.11 mol) and the reaction mixture was stirred for 48 hours at room temperature. The reaction mixture was concentrated under reduced pressure to give **170** as a yellow oil (1.2 g, 92 %; two isomers observed (4:1 A:B)). R_f 0.79 (1:9 methanol:dichloromethane); ν_{max} cm^{-1} (film) 3000-2850 (C-H), 1746 (C=O), 1648 (C=C), 1371 (CH_3), 1227 (C-O), 929 (-CH=CH_2); **isomer A**: δ_H (400 MHz; $CDCl_3$) 7.48 (1H, d, *J* = 6.0 Hz, C*H*N), 6.05-5.94 (1H, m, C*H*=CH_2), 5.39 (1H, dd, *J* = 3.4, 2.4 Hz, $C_{(3)}H$), 5.33 (1H, dq, *J* = 17.5, 1.4 Hz, CH=C$H_{(trans)}$), 5.26 (1H, dq, *J* = 10.4, 1.4 Hz, CH=C$H_{(cis)}$), 5.17 (1H, dd, *J* = 3.6, 2.4 Hz, $C_{(4)}H$), 5.06 (2H, t, *J* = 1.8 Hz, CH_2), 4.69 (1H, dd, *J* = 6.0, 3.4 Hz, $C_{(2)}H$), 4.37-4.21 (3H, m, $C_{(5)}H$, $C_{(6)}H_2$), 2.15 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO); δ_C (100 MHz; $CDCl_3$) 170.7, (C), 169.9 (C), 169.7 (C), 146.3 ($C_{(1)}$H), 133.6 (=CH), 118.2 (=$CH_{2(trans)}$), 117.9 (=$CH_{2(cis)}$), 81.3 ($C_{(2)}$H), 80.4 ($C_{(5)}$H), 79.0 ($C_{(3)}$H), 78.1 ($C_{(4)}$H), 75.6 ($CH_{2(cis)}$), 75.3 ($CH_{2(trans)}$), 63.4 ($C_{(6)}H_2$), 20.9 (CH_3), 20.8 (CH_3), 20.8 (CH_3); **isomer B**: δ_H (400 MHz; $CDCl_3$) 6.86 (1H, d, *J* = 4.4 Hz, C*H*N), 6.05-5.94 (1H, m, C*H*=CH_2), 5.39 (1H, m, $C_{(3)}H$), 5.33 (1H, ddt, *J* = 17.5, 1.4, 1.4 Hz, CH=C$H_{(trans)}$), 5.26 (1H, ddt, *J* = 10.4, 1.4, 1.4 Hz, CH=C$H_{(cis)}$), 5.15 (1H, dd, *J* = 4.4, 2.1 Hz, $C_{(2)}H$), 5.06 (1H, t, *J* = 1.8 Hz, $C_{(4)}H$), 5.06 (2H, t, *J* = 1.8 Hz, CH_2), 4.37-4.21 (3H, m, $C_{(5)}H$, $C_{(6)}H_2$), 2.15 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO); δ_C (100 MHz; $CDCl_3$) 170.7, (C), 169.9 (C), 169.7 (C), 149.3 ($C_{(1)}$H), 133.6 (=CH), 118.2 (=$CH_{2(trans)}$), 117.9 (=$CH_{2(cis)}$), 82.0 ($C_{(2)}$H), 80.4 ($C_{(5)}$H), 79.0 ($C_{(3)}$H), 77.8 ($C_{(4)}$H), 75.6 ($CH_{2(cis)}$), 75.3 ($CH_{2(trans)}$), 63.1 ($C_{(6)}H_2$), 20.9 (CH_3), 20.8 (CH_3), 20.8 (CH_3); m/z [FAB^+] 344.0 (M^++H, 100 %) [found 344.1332 $C_{15}H_{22}NO_8$ expected 344.1345].

_N_-Prop-2-enylphthalimide 174[149]



Allyl bromide (1.1 mL, 12 mmol) was added dropwise to a solution of phthalimide potassium salt **173** (2.8 g, 15 mmol) in anhydrous dimethylformamide (100 mL). The reaction mixture was stirred at 50 °C for 17 hours and the solvent was evaporated. Dichloromethane (50 mL) was added to the remaining mixture and the solution was washed with water (2 x 50 mL) and brine (50 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica using dichloromethane as solvent gave *N*-prop-2-enylphthalimide **174** (2.1 g, 94 %) as a white solid. m.p. 63 °C (lit. m.p. 66-67 °C)[149]; R_f 0.65 (dichloromethane); ν_{max} cm^{-1} (film) 3100-3000 (=C-H), 3000-2850 (C-H), 1700 ($C{=}O_{amide}$), 948 (-CH=CH_2); δ_H (400 MHz; $CDCl_3$) 7.90-7.74 (4H, m, Ar*H*), 5.92 (1H, ddt, *J* = 17.1, 10.2, 5.7 Hz, C*H*=CH_2), 5.28 (1H, dq, *J* = 17.1, 1.5 Hz, CH=C$H_{(trans)}$), 5.23 (1H, dq, *J* = 10.1, 1.5 Hz, CH=C$H_{(cis)}$), 4.33 (2H, dt, *J* = 5.7, 1.5 Hz, NCH_2); δ_C (100 MHz; $CDCl_3$) 170.0 (2 x C), 134.0 (2 x ArCH), 131.5 (2 x ArCH), 132.1 (2 x C), 123.4 (CH=), 117.8 (CH_2=), 40.1 (CH_2); m/z [FAB^+] 188.1 (M^++H, 100 %).

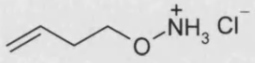
_N_-(But-3-enyloxy)phthalimide 179[115]



Diethyl azodicarboxylate (2.3 mL, 13 mmol) was added dropwise to a solution of butene-1-ol (1.0 mL, 12 mmol), *N*-hydroxyphthalimide **164** (1.9 g, 12 mmol) and triphenylphosphine (3.0 g, 12 mmol) in anhydrous tetrahydrofuran (50 mL) at room temperature. The reaction mixture was stirred for 24 hours under nitrogen and concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 10:90) as eluent gave butenoxy-phthalamide **179** (1.9 g, 77 %) as a pale yellow oil. R_f 0.49 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3100-3000 (ArH), 3000-2850 (C-H), 1789 (NC=O), 1731 ($C{=}O_{amide}$),

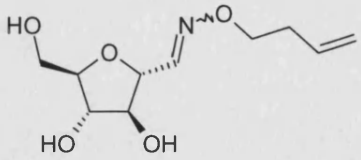
986 (-CH=CH_2); δ_H (400 MHz; $CDCl_3$) 7.85-7.72 (4H, m, Ar*H*), 5.87 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, C*H*=CH_2), 5.19 (1H, dq, *J* = 17.1, 1.5 Hz, CH=C*H*$_{(trans)}$), 5.10 (1H, dq, *J* = 10.2, 1.5 Hz, CH=C*H*$_{(cis)}$), 4.24 (2H, t, *J* = 6.7 Hz, CH_2O), 2.55 (2H, qt, *J* = 6.7, 1.5 Hz, CH_2CH) ; δ_C (100 MHz; $CDCl_3$) 163.6 (2 x C), 134.5 (2 x ArCH), 133.2 (2 x ArCH), 129.0 (2 x C), 123.6 (CH=), 117.6 (CH_2=), 77.3 (CH_2), 32.6 (CH_2); m/z [FAB^+] 218.0 (M^++H, 100 %) [found 218.08148 $C_{12}H_{12}NO_3$ expected 218.0817].

_O_-But-3-enylhydroxylamine hydrochloride salt 181



N-(But-3-enyloxy)phthalimide **179** (1.8 g, 8.3 mmol) and hydrazine hydrate (0.80 mL, 27 mmol) in ethanol (4 mL) were heated under reflux for two hours and poured into a solution of 3 % aqueous sodium carbonate. The reaction mixture was extracted with dichloromethane (3 x 15 mL), washed with water (10 mL), dried with anhydrous magnesium sulfate and filtered. Hydrochloric acid in methanol (4 M, 7.0 mL, 28 mmol) was added forming a white precipitate and the solvent was removed to give *O*-but-3-enylhydroxylamine hydrochloride **181** (0.79 g, 77 %). δ_H (400 MHz; DMSO-d_6) 10.98 (3H, m, N*H*$_3$), 5.77 (1H, ddt, *J* = 17.1, 10.1, 6.5 Hz, C*H*=CH_2), 5.15 (1H, dq, *J* = 17.1, 1.5 Hz, CH=C*H*$_{(trans)}$), 5.07 (1H, dq, *J* = 10.1, 1.5 Hz, CH=C*H*$_{(cis)}$), 4.05 (2H, t, *J* = 6.5 Hz, CH_2O), 2.36 (2H, qt, *J* = 6.5, 1.5 Hz, CH_2CH); δ_C (100 MHz; DMSO-d_6) 134.4 (CH=), 117.9 (CH_2=), 77.5 (CH_2), 32.0 (CH_2); m/z [FAB^+] 88.1 (M^++H, 100 %).

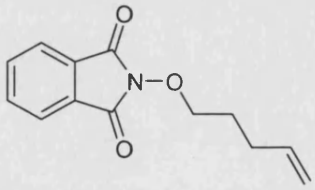
2,5-Anhydro-1-(but-3-enyl)oxime-*D*-mannitol 177



A solution of *O*-butenehydroxylamine hydrochloride **181** (0.79 g, 6.4 mmol) in dimethylformamide (10 mL) was added *via* a cannula to a solution of 2,5-anhydro-*D*-mannose (0.89 g, 4.9 mmol) in dimethylformamide (30 mL). Pyridine (0.80 mL, 9.9 mmol) was added and the reaction mixture was stirred for 20 h at room temperature. After concentration, the residue was purified by flash chromatography on silica using a gradient of methanol:dichloromethane (0:100 → 10:90) as eluent affording butene-oxime

177 as a yellow oil (0.44 g, 36 %; two isomers observed (4:1 A:B)). R_f 0.41 (1:9 methanol:dichloromethane); ν_{max} cm^{-1} (film) 3392 (bs, O-H), 3000-2850 (C-H), 1639 (C=N-O), 1043 (CH_2-OH), 917 (-CH=CH_2); **isomer A**: δ_H (400 MHz; Methanol-d_3) 7.45 (1H, d, *J* = 7.6 Hz, C*H*N), 5.86 (1H, ddt, *J* = 17.5, 10.4, 7.1 Hz, C*H*=CH_2), 5.16-5.04 (2H, m, CH=CH_2), 4.33 (1H, dd, *J* = 7.6, 5.7 Hz, $C_{(2)}H$), 4.16-4.03 (4H, m, OCH_2, $C_{(3)}H$ and $C_{(4)}H$), 3.91 (1H, dt, *J* = 5.2, 3.3 Hz, $C_{(5)}H$), 3.72 (1H, dt, *J* = 11.8, 3.3 Hz, $C_{(6a)}H$), 3.68 (1H, dt, *J* = 11.8, 5.2 Hz, $C_{(6b)}H$), 2.48-2.39 (2H, m CH_2CH=); δ_C (100 MHz; Methanol-d_3) 148.9 ($C_{(1)}$H), 134.6 (=$CH_{(cis)}$), 134.5 (=$CH_{(trans)}$), 115.8 (=$CH_{2(trans)}$), 115.7 (=$CH_{2(cis)}$), 84.7 ($C_{(5)}$H), 81.1 ($C_{(2)}$H), 79.9 (CH), 77.2 (CH), 73.2 ($CH_{2(cis)}$), 72.8 ($CH_{2(trans)}$), 61.7 ($C_{(6)}H_2$), 33.4 ($CH_{2(cis)}$), 33.2 ($CH_{2(trans)}$); **isomer B**: δ_H (400 MHz; Methanol-d_3) 6.83 (1H, d, *J* = 4.7 Hz, C*H*N), 5.86 (1H, ddt, *J* = 17.5, 10.4, 7.1 Hz, C*H*=CH_2), 5.16-5.04 (2H, m, CH=CH_2), 4.97 (1H, dd, *J* = 4.7, 1.9 Hz, $C_{(2)}H$), 4.16-4.03 (5H, m, OCH_2, $C_{(3)}H$, $C_{(4)}H$ and $C_{(5)}H$), 3.72 (1H, dt, *J* = 11.8, 3.3 Hz, $C_{(6a)}H$), 3.68 (1H, dt, *J* = 11.8, 5.2 Hz, $C_{(6b)}H$), 2.48-2.39 (2H, m CH_2CH=); δ_C (100 MHz; Methanol-d_3) 151.8 ($C_{(1)}$H), 134.6 (=$CH_{(cis)}$), 134.5 (=$CH_{(trans)}$), 115.8 (=$CH_{2(trans)}$), 115.7 (=$CH_{2(cis)}$), 86.8 ($C_{(5)}$H), 80.7 (CH), 80.4 ($C_{(2)}$H), 77.7 (CH), 73.2 ($CH_{2(cis)}$), 72.8 ($CH_{2(trans)}$), 62.0 ($C_{(6)}H_2$), 33.4 ($CH_{2(cis)}$), 33.2 ($CH_{2(trans)}$); m/z [FAB$^+$] 232.1 (M^++H, 100 %) [found 232.11789 $C_{10}H_{18}NO_5$ expected 232.1185].

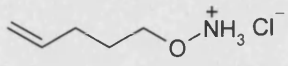
***N*-(Pent-4-enyloxy)phthalimide 180**[115]



Diethyl azodicarboxylate (4.2 mL, 21 mmol) was added dropwise to a solution of pent-4-ene-1-ol (2.0 mL, 19 mmol), *N*-hydroxyphthalimide **164** (3.2 g, 19 mmol) and triphenylphosphine (6.1 g, 23 mmol) in anhydrous tetrahydrofuran (50 mL) at room temperature. The reaction mixture was stirred for 20 hours under nitrogen, concentrated under reduced pressure. Purification by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 20:80) as eluent gave pentenoxy phthalamide **180** as a pale yellow oil. R_f 0.59 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 2979, 2952 (C-H), 1732 (C=O), 1641 (C=C), 1187 (C-O), 878 (-CH=CH_2); δ_H (400 MHz; $CDCl_3$) 7.91-7.35 (4H, m, Ar*H*), 5.87 (1H, ddt, *J* = 16.9, 10.0, 6.8 Hz, C*H*=CH_2), 5.13 (1H, dq, *J* = 16.9,

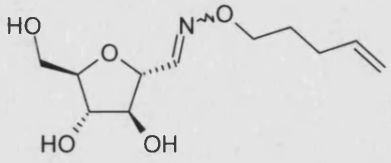
1.8 Hz, CH=C*H*$_{(trans)}$), 5.04 (1H, dq, *J* = 10.0, 1.8 Hz, CH=C*H*$_{(cis)}$), 4.25 (2H, t, *J* = 6.8 Hz, C*H*$_2$O), 2.32 (2H, qt, *J* = 6.8, 1.8 Hz, C*H*$_2$CH=), 1.92 (2H, qn, *J* = 6.8 Hz, CH$_2$C*H*$_2$CH$_2$); δ_C (100 MHz; $CDCl_3$) 163.7 (2 x C), 137.4 (2 x ArCH), 134.5 (2 x ArCH), 129.0 (2 x C), 123.5 (=CH), 115.6 (=CH$_2$), 77.8 (CH$_2$), 29.7 (CH$_2$), 27.4 (CH$_2$); m/z [FAB$^+$] 232.0 (M$^+$+H, 70 %) [found 232.09747 $C_{13}H_{14}NO_3$ expected 232.0974].

_O_-Pent-4-enylhydroxylamine hydrochloride salt 182



N-(Pent-4-enyloxy)phthalimide **180** (4.0 g, 17 mmol) and hydrazine hydrate (1.7 mL, 56 mmol) in ethanol (20 mL) were heated under reflux for two hours and poured into a solution of 3 % aqueous sodium carbonate which was extracted with dichloromethane (3 x 30 mL), washed with water (30 mL), dried with anhydrous magnesium sulfate and filtered. Hydrochloric acid in methanol (4 M, 10 mL, 40 mmol) was added forming a white precipitate and the solvent was removed to give *O*-pent-4-enylhydroxylamine hydrochloride **182** (1.9 g, 79 %). δ_H (400 MHz; DMSO-d_6) 10.98 (3H, m, N*H*$_3$), 5.77 (1H, ddt, *J* = 17.1, 10.1, 6.5 Hz, C*H*=CH$_2$), 5.15 (1H, ddt, *J* = 17.1, 1.5, 1.5 Hz, CH=C*H*$_{(trans)}$), 5.07 (1H, ddt, *J* = 10.1, 1.5, 1.5 Hz, CH=C*H*$_{(cis)}$), 4.05 (2H, t, *J* = 6.5 Hz, C*H*$_2$O), 2.36 (2H, dtt, *J* = 6.5, 6.5, 1.5 Hz, C*H*$_2$CH) 1.80-1.68 (2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (100 MHz; DMSO-d_6) 134.4 (=CH), 117.9 (=CH$_2$), 77.5 (CH$_2$), 32.0 (CH$_2$), 25.1 (CH$_2$); m/z [EI$^+$] 103.0 (M$^+$+H, 8 %).

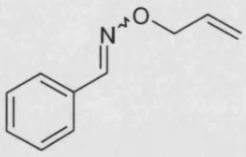
2,5-Anhydro-1-(pent-4-enyl)oxime-*D*-mannitol 178



A solution of *O*-pent-4-enylhydroxylamine hydrochloride **182** (2.4 g, 17 mmol) in dimethylformamide (90 mL) was added *via* a cannula to a solution of 2,5-anhydro-*D*-mannose (2.6 g, 15 mmol) in dimethylformamide (30 mL). Pyridine (2.2 mL, 26 mmol) was then added and the reaction mixture was stirred for 17 h at room temperature. After concentration, the residue was purified by flash chromatography on silica using a gradient of methanol:dichloromethane (0:100 → 10:90) as eluent affording pentene-

oxime **178** as a yellow oil (1.4 g, 39 %; two isomers observed (4:1 A:B)). R_f 0.50 (1:9 methanol:dichloromethane); ν_{max} cm^{-1} (film) 3392 (O-H),2936 (C-H), 1641 (C=N), 1441 (C-H), 1046 (CH_2-OH), 914 (-CH=CH_2); **isomer A**: δ_H (400 MHz; Methanol-d_3) 7.45 (1H, d, *J* = 7.4 Hz, C*H*N), 5.88 (1H, ddt, *J* = 16.7, 10.0, 6.7 Hz, C*H*=CH_2), 5.05 (1H, m, CH=C$H_{(trans)}$), 5.01-4.97 (1H, m, CH=C$H_{(cis)}$), 4.33 (1H, dd, *J* = 7.4, 5.7 Hz, $C_{(2)}H$), 4.13-4.04 (4H, m, OCH_2, $C_{(3)}H$ and $C_{(4)}H$), 3.91 (1H, dt, *J* = 5.5, 3.5 Hz, $C_{(5)}H$), 3.72 (1H, dt, *J* = 11.9, 3.5 Hz, $C_{(6a)}H$), 3.68 (1H, dt, *J* = 11.9, 5.5 Hz, $C_{(6b)}H$), 2.18-2.12 (2H, m CH_2CH=), 1.82-1.72 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz; Methanol-d_3) 148.7 ($C_{(1)}$H), 137.9 (=CH), 114.0 (=$CH_{2(trans)}$), 113.9 (=$CH_{2(cis)}$), 84.6 ($C_{(5)}$H), 81.1 ($C_{(2)}$H), 79.9 (CH), 77.2 (CH), 73.3 ($CH_{2(cis)}$), 72.9 ($CH_{2(trans)}$), 61.7 ($C_{(6)}H_2$), 29.7 ($CH_{2(cis)}$), 29.6 ($CH_{2(trans)}$), 28.1 ($CH_{2(cis)}$), 28.0 ($CH_{2(trans)}$). **isomer B**: δ_H (400 MHz; Methanol-d_3) 6.82 (1H, d, *J* = 5.3 Hz, C*H*N), 5.88 (1H, ddt, *J* = 16.7, 10.0, 6.7 Hz, C*H*=CH_2), 5.05 (1H, m, CH=C$H_{(trans)}$), 5.01-4.97 (2H, m, CH=C$H_{(cis)}$ and $C_{(2)}H$), 4.13-4.04 (5H, m, OCH_2, $C_{(3)}H$, $C_{(4)}H$ and $C_{(5)}H$), 3.72 (1H, dt, *J* = 11.9, 3.5 Hz, $C_{(6a)}H$), 3.68 (1H, dt, *J* = 11.9, 5.5 Hz, $C_{(6b)}H$), 2.18-2.12 (2H, m CH_2CH=), 1.82-1.72 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz; Methanol-d_3) 151.6 ($C_{(1)}$H), 137.9 (=CH), 114.0 (=$CH_{2(trans)}$), 113.9 (=$CH_{2(cis)}$), 86.9 ($C_{(5)}$H), 80.8 (CH), 80.2 ($C_{(2)}$H), 77.7 (CH), 73.3 ($CH_{2(cis)}$), 72.9 ($CH_{2(trans)}$), 62.0 ($C_{(6)}H_2$), 29.7 ($CH_{2(cis)}$), 29.6 ($CH_{2(trans)}$), 28.1 ($CH_{2(cis)}$), 28.0 ($CH_{2(trans)}$); m/z [FAB^+] 246.1 (M^++H, 100 %) [found 246.13515 $C_{11}H_{20}NO_5$ expected 246.1341].

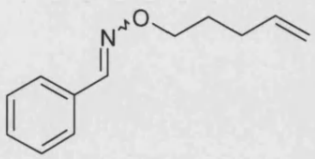
***O*-(Prop-2-enyl)benzaldehydoxime 188**



A solution of *O*-prop-2-enylhydroxylamine hydrochloride **166** (1.9 g, 17 mmol) in dimethylformamide (25 mL) was added to benzaldehyde (1.3 mL, 13 mmol) in dimethylformamide (25 mL). Pyridine (2.1 mL, 26 mmol) was then added and the reaction mixture was stirred for 16 h at room temperature. After concentration, the residue was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 5:95) as eluent affording propene-oxime **188** as a colourless oil (1.9 g, 89 %). R_f 0.89 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3081, 3027 (=CH), 2989, 2921, 2868 (C-H), 1639 (C=N), 1448 (C-H), 1039 (C-O), 846 (-CH=CH_2); δ_H (400

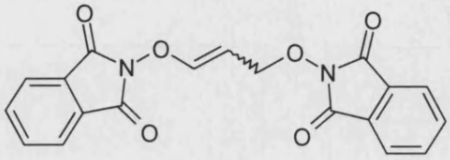
MHz; $CDCl_3$) 8.17 (1H, s, C*H*N), 7.65-7.62 (2H, m, Ar*H*), 7.43-7.40 (3H, m, Ar*H*), 6.11 (1H, ddt, J = 17.1, 10.3, 5.5 Hz, C*H*=CH_2), 5.41 (1H, dq, J = 17.1, 1.6 Hz, CH=C$H_{(trans)}$), 5.31 (1H, dq, J = 10.3, 1.6 Hz, CH=C$H_{(cis)}$), 4.74 (2H, dt, J = 5.5, 1.6 Hz, CH_2CH=); δ_C (100 MHz; $CDCl_3$) 148.9 (CH=N), 134.1 (C), 132.3 (ArCH), 129.8 (2 x ArCH), 128.7 (2 x ArCH), 127.1 (=CH), 118.0 (=CH_2), 75.2 (CH_2); m/z [EI^+] 161.1 (M^+, 77 %).

_O_-(Pent-4-enyl)benzaldehydoxime 189



A solution of *O*-pent-4-enylhydroxylamine hydrochloride **182** (0.20 g, 1.5 mmol) in dimethylformamide (10 mL) was added to benzaldehyde (0.11 mL, 1.1 mmol) in dimethylformamide (10 mL). Pyridine (0.18 mL, 2.2 mmol) was then added and the reaction mixture was stirred for 17 h at room temperature. After concentration, the residue was purified by flash chromatography on silica using a gradient of diethyl ether:hexane (0:100 → 20:80) as eluent affording pentene-oxime **189** as a colourless oil (0.17 g, 86 %). R_f 0.90 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3078, 3028 (=CH), 2934, 2873 (C-H), 1641 (C=N), 1447 (C-H), 1056 (C-O), 913 (-CH=CH_2); δ_H (400 MHz; $CDCl_3$) 8.12 (1H, s, C*H*N), 7.65-7.58 (2H, m, Ar*H*), 7.46-7.33 (3H, m, Ar*H*), 5.89 (1H, ddt, J = 17.0, 10.0, 6.6 Hz, C*H*=CH_2), 5.10 (1H, dq, J = 17.0, 1.6 Hz, CH=C$H_{(trans)}$), 5.03 (1H, dq, J = 10.0, 1.6 Hz, CH=C$H_{(cis)}$), 4.23 (2H, t, J = 6.6, CH_2O), 2.23 (2H, dtt, J = 7.2, 6.6, 1.6 Hz, CH_2CH=), 1.87 (2H, tt, J = 6.6, 7.2 Hz, $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 148.4 (CH=N), 138.1 (C), 132.5 (ArCH), 129.7 (2 x ArCH), 128.7 (2 x ArCH), 127.0 (=CH), 114.9 (=CH_2), 73.7 (CH_2), 30.1 (CH_2), 28.4 (CH_2); m/z [FAB^+] 190.0 (M^++H, 16 %) [found 190.12368 $C_{12}H_{16}NO$ expected 190.1123].

_N_-(3-(Oxyphthalimide)prop-2-enyloxy)phthalimide 192



_N_-(Prop-2-enyloxy)phthalimide **163** (33 mg, 0.16 mmol) in deuterated chloroform (4.0 mL) was added to second generation Grubbs catalyst (0.13 g, 0.15 mmol). The reaction mixture was agitated by vertical rotation at 45 °C for 90 minutes and was washed with deuterated chloroform (3 x 5 mL). Following concentration, the residue was purified by column chromatography affording compound **192** as a colourless oil (15 mg, 25 %). R_f 0.44 (1:1 diethyl ether:hexane); ν_{max} cm^{-1} (film) 3029, 3028 (=CH), 2955, 2924, 2850 (C-H), 1726 (C=O), 1463 (C-H), 969 (=CH), 696 (=CH); δ_H (400 MHz; $CDCl_3$) 7.89-7.69 (4H, m, Ar$H_{phthalimide}$), 7.38-7.23 (4H, m, Ar$H_{phthalimide}$), 6.67 (1H, d, J = 15.8 Hz, OCH=), 6.46 (1H, dt, J = 15.8, 7.0 Hz, CH_2CH=), 4.87 (2H, dd, J = 7.0, 1.2 Hz, CH_2CH=); δ_C (100 MHz; $CDCl_3$) 163.9 (4 x C), 137.6 (=CHO), 135.8 (4 x C), 134.5 (2 x ArCH), 128.7 (2 x ArCH), 126.9 (2 x ArCH), 123.6 (2 x ArCH), 122.0 (=CH), 78.7 (CH_2).

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